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Archives of Internal Medicine

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MEDICAL SOCIAL ASPECTS IN PRACTICE

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BOSTON

A considerable fraction of the successful care and treatment of patients and, undoubtedly, the prevention of much illness is to be identified with the proper consideration of sociologic factors. The case of every patient who consults a physician has a medical social aspect. This social component of medicine may vary widely in importance, but frequently it plays a major rôle in diagnosis, prognosis and treatment and in the prevention of disease and unhappiness. Every one is constantly confronted with social problems which he settles without great difficulty or to which he soon adjusts himself; but the problems may become of medical significance, so that, as Parry of Bath indicated late in the eighteenth century, it is often more important to know what kind of a patient has a disease than what disease the patient has. Lack of thoroughness and imperfect skill are causes of many errors in the prevention, diagnosis and prognosis of disease and in the treatment of patients. The diagnosis of the person is often neglected when the diagnosis of disease is considered in detail.

The medical social aspects of each case are intertwined intimately with the psychiatric, environmental, economic, hereditary and allied aspects. For centuries physicians have recognized the importance of such conditions in prescribing wisely for patients; yet seldom are physicians scholars of this subject. This problem is not new. James Jackson, the second Herseian professor of the theory and practice of psychic at Harvard wrote in 1861, when he was 84 years old:

> Among the sciences, the principles of which it is necessary for the physician to understand is that of human nature; or, otherwise described, the principles of the philosophy of the human mind and heart. This strictly and properly is a branch of human physiology. It is, however, a branch which is ordinarily not brought into view. The mind has much to do with the health of the body.

He indicates clearly in his various publications the importance of studying and applying knowledge concerning all aspects of the patient's life.

Although the physician in private practice has often attempted to consider faulty character, undesirable community life, unwholesome

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard University Medical School.

human relations and other aspects of the patient's self, knowledge concerning such subjects is not frequently obtained and applied. Certain of the more obvious medical social problems are, of course, usually considered, for example, financial complications, in advising a sojourn in Florida, or religious dietary restrictions, in advising food for persons of certain faiths. Able young physicians soon appreciate that social aspects form an important feature of many cases and thus they often wish that they knew more concerning patients as individuals. The general practitioner of many years ago acquired this sort of information with ease and utilized it most successfully. There is, of course, no dispute regarding the fact that many physicians with insight and ingenuity do attend admirably to the social aspects of their cases, but more organization and diffusion of knowledge concerning medical social problems, with the development of intelligent methods of study and the acquisition of more real knowledge, would be a great step in advance.

The character of medical practice today, with its division into specialties, and the many trends of modern times do not favor the doctor becoming intimately acquainted with his patient's personal life without conscious effort, as the physician of one hundred years ago did almost automatically. Today there is vastly more sound knowledge concerning the influence on health of living conditions and the problems of life; but living conditions have become much more complex with industrialization, urbanization, the results of invention and the development of many modern customs leading to haste and often to waste. Thus, the physician today needs not only to have such knowledge concerning social problems as was available to the physician of years ago, but he must have much more information of this sort and apply it thoroughly. The science dealing with the relation between human behavior and health is in its infancy, and the progressive physician should attempt to advance medical knowledge in this direction as much as he has advanced that concerning organic disease within the past quarter century.

The development of hospital social service, which is now wisely termed medical social work in hospitals, was begun particularly because of the necessity and desirability of the division of labor among the medical and allied staffs of hospitals. It became evident that in institutions lack of time, insufficient training or inability prevented the physician from carefully considering the social component of medicine in each case. Hospital social service has become a potent means for more accurate diagnosis, more effective treatment and the prevention of suffering, but it is effective directly in relation to the quality of the medical work. High grade medical work permits good social work, and vice versa. It has taken time for some physicians to realize that many failures in treatment at hospitals are due, in part, to elements outside the limits

of what might be called conventional medical practice; the same is, of course, true in private practice. The efforts of medical social workers devoting themselves to the study and understanding of social conditions and of physicians taking full charge of all aspects of the patient must be closely related. The physician must lead. The social worker contributes to the understanding of the personal and environmental factors in the health of patients; she may aid in carrying out treatment and help in many ways, but the physician must remain the chief, and the social worker must cooperate closely with his program. Intimate relations between the various clinics of a hospital are essential. The social clinic (social service department) improves the work of all the clinics and should be on the same plane as other clinics. Thus, the importance of social problems will be fully appreciated, and the patient will receive the greatest possible benefit.

The development of medical social work in hospitals during the past quarter century has been one important factor in bringing to the physician knowledge concerning the social component of medicine. It has helped to awaken him to the importance of these problems, which, perhaps, he tended to neglect during the era of rapid development of scientific medicine. The work of psychiatrists, educators and other persons interested in the problems of human welfare is also responsible for a better understanding of the vast variety of medical social problems with which the physician is confronted. Thus, whereas it was once recognized that a phase of medicine practiced by the good physician was lacking in institutional work, and hospital social service was developed largely to fill that need, the technic of social workers has become so perfected that not only a knowledge of their methods, but also the information which they hold, can aid physicians in seeking the social history and applying such knowledge in their private practice.

The physician in private practice at present rarely has recourse to an expert medical social worker, although he may call on medical specialists, such as the roentgenologist or the heart specialist, for aid. The physician himself must attend to the social aspects of his patient's case, although he may receive help if he knows how to seek it, especially from the psychiatrist, clergyman and the schoolmaster. Seldom has the physician received training in the subject, and he must learn for himself not only the significance of medical social problems but methods of studying them. He must become acquainted with community resources. He must learn how to teach persons the most beneficial way of conducting certain careers and the business of actual living, which is to be distinguished from the preliminaries of living, such as education and the obtaining of shelter, food and other supplies. All such matters constantly confront persons for decisions. That art which lies

particularly in keeping the peace with those with whom one is thrown or with one's mental and physical environment must be taught in each case so as to be suitable for the given person. In other words, recognition must be given to the rhythm of life, not only to the factors that affect the ebb and flow, but also to the surging and conflicting currents. It is the study of such matters that leads the wise physician to success in treatment.

One can still find physicians who take the view that medical social work concerns only the poor and friendless. They forget that such work is not concerned with charity or spiritual welfare, as is that performed by the church. The social problems in private practice are as numerous and frequent as in hospital practice and are often more complex and difficult to correct. This is because the higher the social order of the patient, the more complicated the social issues and intricacies of life are apt to become. To appreciate this, one only has to think of the greater complexities arising in the life of a person with servants, children in private schools, many friends and multiple social, professional and business obligations, as contrasted with the life of a day laborer; yet both may be confronted with basically the same medical social problems.

REPORT OF CASES

The following three cases, presented in outline, illustrate the importance of the social component of medicine in practice. The first case illustrates the failure of that prescription of great therapeutic importance, rest, because of lack of complete understanding of the patient, and then illustrates the success obtained with this prescription after the social aspects were known and the knowledge was applied.

CASE 1.—Mrs. A., 44 years of age, the wife of the president of a large industrial corporation, had mild atrophic (rheumatoid) arthritis of five years' duration. Among other therapeutic measures, rest seemed important. She admitted that she always felt tired, but insisted that she did nothing to get tired. She recognized that she had many duties to perform in relation to the care of her two daughters, her relatives, the management of her house and suburban estate and charitable and social organizations, but she said, "They are pleasant matters to attend to, and surely they cannot be the cause of fatigue." Her physician, who had seen her only in his office, without any further information about her daily life, the nature of her home or her attitude toward people or affairs, said to her, "You must rest an hour each morning and afternoon." Time passed, and she was no better. Another physician called into consultation believed that rest, in the complete sense of the word, was essential, and that although the patient had lain down two hours a day she had secured little rest. He visited her home; he observed its character, the patient's behavior and the behavior of the people with whom she came in contact daily. A few salient facts from among the many obtained were as follows: The only time the house was quiet enough for her to write personal letters was late in the evening. Mrs. A. admitted that she feared that her social prestige

would be diminished if her correspondence was not voluminous. She often had breakfast with her husband at 7:30 a. m., for it was only at breakfast that he had time to give her directions about their handsome estate, of which they were proud and which they wished to keep in splendid condition. Many days in the week she gave directions to the gardener and took pains to see that the work was properly completed. "But," she said, "I never have time to be thorough about these matters; I crave time to read about them, but that would be selfish."

Mr. A. was physically strong and led an intensive business life. He often brought home business guests for dinner on a moment's notice, and was anxious to entertain socially at frequent intervals. He was never tired and did not at first understand why his wife should feel fatigued. He expected her to supervise and help in a meticulous way in many matters of mutual interest and to send many telegrams and messages concerning business. She was often called to the telephone fifteen times a day. At the beginning of the day she was apt to hurry to complete the household duties and became irritated when there was delay. She usually had an appointment away from home soon after 9 o'clock. Eight committees demanded her presence. She got along well with the members of all except one—the one which she considered the most important and which met frequently. On this committee were the wives of her husband's business associates and also of his competitors. As chairman, she could not do what seemed wise for fear of causing unpleasant situations which would reflect on her husband's business.

Her two daughters, aged 18 and 16 years, respectively, caused anxiety. The elder presented a peculiar behavior problem. Mrs. A. said that she "just failed to understand her and the more she tried to help the worse the child behaved." The younger daughter was thin and ate an improper diet largely because she "must be slim." At meals Mrs. A. always antagonized this child, which, in turn, often led Mrs. A. to have transient emotional outbursts. She believed that she enjoyed luncheon parties and "knew she simply must attend many of them." Her mother-in-law lived in an annex to the house with her own retinue. She was 85 years of age and had senile dementia. Mrs. A. felt obliged to see her daily, for her husband's sake, and to see that her servants performed their duties properly.

The rests which Mrs. A. had taken consisted of lying down for a total of about two hours a day with the telephone beside her couch, which she answered when the bell rang. During these "rests" she made memoranda with pencil and sometimes talked with people she "had to see." An endless array of simple problems concerning servants, friends, charities, horticulture and other matters were disclosed. Mrs. A. believed that she never could say "No" to requests or invitations, as that would be selfish, and her husband wanted her to be prominent and to accept every opportunity for social contact. She recognized that she attended to many matters, but believed that she was not capable of completing anything worth while.

Conversation with Mr. A showed that at heart he was sympathetic. He said that he had simply never stopped to think "what he was asking of her." He agreed to help arrange matters so that she could obtain true rest, tranquillity with relaxation, the minimum of psychic trauma and an opportunity to lead a well planned life. The physiologic mechanism of chronic fatigue and the influence of fatigue and rest on the functions of the body were described so that both Mr. and Mrs. A. fully appreciated the reasons for, and the importance of, rest for Mrs. A. This conversation made them cooperative at once. They were highly intelligent and fundamentally sensible persons. Arrangements were made so that Mrs. A. spoke over the telephone only at definite times each day. Mr. A. saw

to it that none of his business matters were handled by his wife, although he made it a point to keep her in as close touch with such affairs as before. She agreed to resign from certain committees and was easily persuaded to recognize that careful attention to a few matters would be more likely to lead to accomplishment than a diversification of efforts. Arrangements were made for certain household matters which she had formerly supervised to be attended to by a servant. She was instructed to answer practically no invitations verbally, thus making it possible for her to reflect and to answer more easily and more often in the negative. She was taught how to start the day slowly.

She agreed not to discuss the behavior of her daughters with them for eight weeks. With a physician's assistance, which included advice to Mrs. A., both children soon improved, much to the happiness of the family. These and other matters were adjusted to the delight of all members of the family, with resulting improvement in the health of each. Mrs. A. then had a calm life; she truly rested attempting to sleep one hour each afternoon. She was taught how to relax all the muscles of her body and was instructed to practice this several times each day. Soon she found that she had time to enjoy the beautiful garden and realized that previously it had been more of a drudgery than a pleasure. "Employment is nature's best physician," Galen wrote, "and essential to human happiness." Mrs. A. had ample employment, yet learned to carry out her activities with much greater tranquillity than before. She admitted that she accomplished more in a thorough manner under her new régime. Her daily life was changed from one of intensity and often relatively useless activity, with frequent irritability, to one of happiness for herself and her family. Not only was she improved much in all ways, but as a result of her improvement her children are better and her husband is happier; indeed, all of them are enjoying life more than before.

The course of events outlined permitted Mrs. A. to obtain much more rest without lying down for a longer period. This was accomplished only after prolonged study of the social factors and after many conversations with the patient and her family and friends. The physician must appreciate that in order to unravel such problems as that presented in Mrs. A's case, and to succeed in accomplishing the object desired, a large amount of work is necessary. Treatment consisted of much more than simply saying, "Rest." It necessitated an appreciation of the sociologic factors, an understanding of her home from inspection and the cooperation of her husband and children in particular.

Physicians probably often neglect to recognize that failure in treatment may be due to them rather than to the prescriptions which they give the patient. Lack of imagination and scientific curiosity may often be the cause of their failure. Unfortunately, physicians sometimes indicate that they have no time or patience to attend to the needs of nervous people, that these problems bore them and that such disorders as chronic arthritis are uninteresting. That attitude is unfortunate; the physician should be deeply interested in his patient or else not accept him for care. Therapeutic success depends on treatment carried out thoroughly, intensively and whole-heartedly, with attention to all the aspects of the case. The physician should show a deep interest in

human beings and in their economic and social structure, as well as in their physical and psychic state. The value and importance of such work as the adjustment of Mrs. A.'s life sometimes passes unrecognized, yet does more dramatic work, such as an extensive surgical operation, accomplish more?

In evaluating medical social aspects, it is important not to interpret them in terms of what the physician, personally, would do or like, or in the light of his own life or that of his relatives. Happiness can exist in circumstances that to him may seem intolerable. He must not be prejudiced, and he must have a wide breadth of vision. There is, perhaps, nothing more difficult than to decide wisely what is best for other persons as concerns the art, business and preliminaries of living.

The problem of being beset with the cares of living so that one has no time for life itself is common. The present century is one of restlessness; there is a continuous mood of excitement. Many people have not the least idea why they are in a hurry all day long. One may observe persons of the leisure class rushing through streets, crowding out of trains and the like, as if the most serious and urgent tasks were awaiting them at home. They simply yield to the general movement of the times. This type of problem is one that concerns the medical social aspects of many cases as, for example, the case of Mr. Y.

CASE 2.—Mr. Y., a quick-tempered person with duodenal ulcer, had become repeatedly symptom-free after rest in the hospital and a proper diet. The factory which he supervised had been run satisfactorily. Apparently, his affairs were in good order, and he appeared happy. However, when he was at work the symptoms of duodenal ulcer always returned. The social aspects of his case were at last investigated. His daily life was one of incessant haste; he interviewed certain persons repeatedly because he never remembered to complete his object at one time, and his methods of work were found to be badly organized—papers were constantly mislaid, and he permitted his work to be interrupted unnecessarily. Furthermore, he attended to matters which he admitted did not concern his job, because he used to attend to them years before when he was a foreman in the factory, and his tendency was to run slowly, rather than to walk, as he went from place to place in the factory. He had no hobbies or interests outside of his work, and his home was barren of books and pictures. Each night he worked on problems relating to the factory, never considering his children, and rarely did they or his wife do anything together except eat meals, at which business was the chief topic of conversation.

It seemed that if this state of affairs could be corrected and if the patient could have carefully explained to him the influence of emotions on the digestive organs and functions of the body, as has been so well set forth by Cannon, a start would be made in the prevention of the recurrence of his symptoms. He was taught how to banish from life all superfluities and thus was schooled in the art of having time. The means of escape from his ineffective haste was the resolution not to be swept away by the prevailing current of the age, as though he could not have a will of his own. The habit of systematized work, a preservative of physical and intellectual health, together with regular exercise and brief

periods of rest, was instituted. After a year he was better, but whereas he formerly appeared happy, he now seemed unhappy. The character of his life was studied further. It was learned that for years he had believed that he was not wanted in the social community in which he lived because he had "risen from the ranks," while his neighbors had largely inherited considerable money. This idea was found to be chiefly of his own creation. As time passed, he was urged to accept the invitations of his neighbors and to join in their social life. This was accomplished particularly by the physician explaining the situation to two of the patient's friends, who were most helpful. Within another year he took time for relaxation and exercise with his friends and became much happier. At home his horizon broadened. He continued with the rearrangements regarding his work and increased his social activities; coincidentally with this, the symptoms relating to the ulcer have been slight for two years. Mr. Y. learned much about the art of work, the art of having time and how to fight the battles of life, as the result of the assistance which a physician gave him after a careful study of the medical social aspects of his case.

The able physician must be alert for opportunities to practice preventive medicine. The prevention of unsocial states can lead to an untold amount of good. The following case illustrates how preventable social conditions lead to illness and how important it is for the physician to consider the family as a whole when taking care of one member.

CASE 3.—It was decided that the patient, a 16 year old girl with incipient pulmonary tuberculosis, should be cared for at home. She had devoted parents with, apparently, a good income and two brothers, aged 12 and 14 years, respectively. Their home was neat and contained choice books, nice pieces of china and antique furniture. A glassed-in piazza was built for the benefit of the patient. The two boys were not examined for tuberculosis because, according to their mother, "it did not seem necessary." The mother soon found that she had no time to give to the younger children. Everything was done for the sick girl. She was given expensive food and every attention. The father became anxious and attended to intricate details regarding his daughter. Soon much conversation about expenses arose; a servant was released; the boys heard discussions about economy and learned that nothing could be spared from their sister's needs. The father took on some extra literary work, cut his rest hours and became fatigued and more anxious about finances. Both boys began to receive much lower marks at school than formerly; the elder lost weight, and both appeared tired. The schoolmaster brought this state of affairs to the parents' attention. Examination of the boys revealed no tuberculosis. Another physician was consulted, who confirmed the absence of this disease. However, he learned that the boys had been anxious about their sister for months. They had never had the situation explained to them and expected her to die. They told how they had heard so much about economy that they thought that they could help if they went without their mid-morning lunch at school and ate sparingly at home. The boys felt that they were neglected and longed to have their mother read to them as she had done before their sister was sick. The parents admitted that they were so wrapped up in their daughter's interests that they had neglected to "even think of their sons." The boys had often spent hours at night talking about their sister and wondering how they could help. They believed that their family had lost so much money that they soon

would all be in the almshouse. They obviously became unhappy and suffered from mental anxiety. They even believed that their parents had stopped loving them, and yet they strove to think in what way they could help.

The facts were explained to the boys: Their sister was recovering rapidly; the parents did not have as much money as formerly, but it was extremely unlikely that they would be obliged to change their mode of living in a fundamental way. The mother and father were greatly distressed when they realized how little attention they had given their sons and were deeply touched by the motive of their thoughts. They arranged to give the boys more personal attention and saw to it that they had a proper amount of food. Soon the whole family was happy; the boys gained weight and again did well in their lessons, and before long their sister's tuberculosis was completely arrested.

The psychology of children is an important and large problem and will not be discussed in this article. It is a mistake to make mysteries of illnesses; it is usually wise to inform all members of the household of the facts about a case. One may also note that discussions before children regarding financial depression, family income and the like are apt to be interpreted by them as more serious than the facts demand. Anxiety over financial problems is, of course, common and can lead to many types of medical social problems. Even when reduction of the budget is great, a clear appreciation of the facts, with a wise selection for expenditure, together with an adjusted view of life, can permit happy lives to be led in spite of economic distress.

COMMENT

The matters which I have discussed seem simple, but it may require considerable experience and often much time to obtain medical social information and apply it usefully. Tact and personality play an important rôle, but an acquaintance with the stream of world thought and the actions of human beings, an understanding of "the conflicts of principle," "the meaning of right and wrong" and much other information of this sort are valuable when treating patients whole-heartedly and intensively. As has been noted, the ancients and the physicians in general practice of years ago developed knowledge of the medical social aspects of medicine, and medical social workers in recent times have been responsible for unfolding and clarifying such knowledge. Today there is the problem of how the young physician can obtain modern knowledge concerning the social component of medicine. This is a problem of medical education. It is being studied in a few medical schools where significant teaching of the subject is undertaken. Clinicians have the responsibility of teaching the social aspects of medicine. The need is to permeate the curriculum and to instruct the instructors in the subject. Time will be required to accomplish this. At present in a relatively few clinics special exercises illustrating the value and impor-

tance of medical social work are given. The generation of physicians now in their third decade of life will advance the present knowledge of human behavior and of the intricate effects of social, economic and allied disorders on health. They will be aided by professional medical social workers. An intelligent appreciation of these problems and an understanding of how to correct unsocial situations not only can save suffering, but can lead to the prevention of waste, useless efforts and unhappiness.

Many physicians with ability and insight have always attended to the medical social aspects of cases more or less well, but the important thing to recognize is that careful study and formulation and extension of knowledge in regard to these matters is needed, rather than leaving them to haphazard abilities or to individual interests. The field is a difficult one for reliable scientific study, because it involves all the complications of human life. Even so, physicians will gradually become more and more awakened to the increasing importance of social factors in medicine and will apply modern knowledge of this sort intuitively, not only in the hospital clinic, but also in private practice.

ETIOLOGY OF HODGKIN'S DISEASE

II. SKIN REACTION TO AVIAN AND HUMAN TUBERCULIN PROTEINS IN HODGKIN'S DISEASE

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The etiologic relationship of Hodgkin's disease (lymphogranulomatosis) and tuberculosis remains uncertain. Most of the investigations designed to solve this problem have been the experimental injection of diseased tissues into animals or cultural studies. Injections of "pure" Hodgkin's tissues do not regularly produce tuberculosis in animals, and cultures of the same tissues only occasionally yield a growth of acid-fast bacilli. The reports of L'Esperance [1] claiming that tissues histologically typical of Hodgkin's disease produced tuberculosis in chickens—an animal species not previously used for this purpose—gave a new impetus to such studies. Utz and Keatinge [2] stated that they had confirmatory evidence. Van Rooyen,[3] Garrod,[4] Stewart,[5] Wallhauser [6] and I [7] failed to confirm the findings of L'Esperance.

Numerous early investigators of Hodgkin's disease performed tuberculin tests on some of their patients in an effort to obtain information on the relationship of the two diseases. As early as 1902 Reed [8]

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1. L'Esperance, E.: Experimental Inoculation of Chickens with Hodgkin's Nodes, J. Immunol. **16**:37 (Jan.) 1929; Study of a Case of Hodgkin's Disease in a Child, ibid. **18**:127 (Feb.) 1930; A Case of Pel Ebstein's Syndrome of Tuberculous Origin, ibid. **18**:133 (Feb.) 1930; Studies in Hodgkin's Disease, Ann. Surg. **93**:162 (Jan.) 1931.

2. Utz, L., and Keatinge, L.: Hodgkin's Disease, M. J. Australia **1**:397 (April 4) 1931.

3. Van Rooyen, C. E.: Aetiology of Hodgkin's Disease with Special Reference to B. Tuberculosis Avis, Brit. M. J. **1**:50 (Jan. 14) 1933.

4. Garrod, L. P., in Horder, T., and others: Rose Research on Lymphadenoma, Bristol, England, John Wright & Sons, 1932, p. 105.

5. Stewart, H. L.: Etiologic Studies in Hodgkin's Disease, J. Lab. & Clin. Med. **18**:281 (Dec.) 1932.

6. Wallhauser, A.: Hodgkin's Disease, Arch. Path. **16**:522 (Oct.); 672 (Nov.) 1933.

7. Steiner, P. E.: Hodgkin's Disease: Search for an Infective Agent and Attempts at Experimental Reproduction, Arch. Path. **17**:749 (June) 1934.

8. Reed, D.: On the Pathological Changes in Hodgkin's Disease, with Special Reference to Its Relation to Tuberculosis, Johns Hopkins Hosp. Rep. **10**:133, 1902.

observed that the tuberculin tests performed on five of her eight patients with Hodgkin's disease were negative. Simmons,[9] Steiger,[10] Corbeille,[11] Freer,[12] Bastai [13] and others observed that most of their patients gave negative reactions to tuberculin cutaneous tests. This has been used as evidence that Hodgkin's disease is etiologically unrelated to the tubercle bacillus.

The reports of L'Esperance suggested the possibility that a comparison of the cutaneous reactions to human and avian tuberculins might give valuable information as to the etiologic rôle of the avian tubercle bacillus in Hodgkin's disease. L'Esperance reported the results of such tests performed on twelve patients with various lymphadenopathies. Seven of these gave positive reactions with avian tuberculin. Only four of the seven had lesions histologically characterisic of Hodgkin's disease, so she was not impressed with the specificity of the reaction.

Parker and his co-workers [14] also compared the cutaneous reactions to human and avian tuberculins in a large series of cases of different lymphadenopathies. They reported fewer positive reactions in patients with diseases of the lymphoid and myeloid tissues and with malignant disease than in normal persons and tuberculous patients. They also found more positive reactions to the avian tuberculin than to the human except in the normal group.

As part of a more extensive investigation begun during 1931 on the etiology of Hodgkin's disease, a comparison of the cutaneous reactions to old tuberculin derived from human and avian strains was made on these patients. Later the highly purified tuberculin proteins (avian and human) prepared by Seibert [15] were made available by her for these tests, and were used throughout the remainder of the investigation. With these preparations quantitative tests of sensitization can be performed.

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9. Simmons, C. C.; Hodgkin's Disease, A Pathological Analysis of Nine Cases, J. M. Research **9**:378, 1903.

10. Steiger, O.: Klinik und Pathologie der Lymphogranulomatosis (Paltauf-Sternberg): Beobachtungen und experimentelle Studien bei 9 Fällen von malignem Granulom, Ztschr. f. klin. Med. **79**:452, 1915.

11. Corbeille, C.: Hodgkin's Disease in Children, Minnesota Med. **11**:678 (Oct.) 1928.

12. Freer, W.: Lymphogranulom bei Kindern, Jahrb. f. Kinderh. **123**:145 (March) 1929.

13. Bastai, P.: Ueber die klinische Bedeutung der Tuberkulin Anergie bei malignem Lymphogranulom, Klin. Wchnschr. **7**:1606 (Aug. 19) 1928.

14. Parker, F.; Jackson, H.; Fitz-Hugh, G., and Spies, T.: Studies of Diseases of the Lymphoid and Myeloid Tissues: IV. Skin Reactions to Human and Avian Tuberculin, J. Immunol. **22**:277 (April) 1932.

15. Seibert, F. B., and Munday, B.: The Chemical Composition of the Active Principle of Tuberculin: XV. A Precipitated Purified Tuberculin Protein Suitable for the Preparation of a Standard Tuberculin, Am. Rev. Tuberc. **25**:724 (June) 1932.

The factor of variability of the potency and antigenicity of the test material according to the strain of organism or method of preparation used is eliminated. In this article the results of cutaneous tests performed on most of the patients in the cases reported in a previous communication, as well as on many others, are given.

EXPERIMENTAL WORK

Cutaneous tests with tuberculin protein (Seibert) performed on thirty-five patients with Hodgkin's disease, eleven with leukemia, three with lymphosarcoma, six with carcinoma, nine with tuberculous adenitis and nine with nonspecific adenitis form the basis of this report. In each case—except in some with leukemia—the diagnosis was made by histologic examination of diseased tissue of a lymph node by one or more disinterested, experienced pathologists.

The tuberculin proteins were given intracutaneously in test doses of 0.1 cc. and the result observed in forty-eight hours. The first doses were 0.0001 mg. of the proteins. If there were no reactions to these doses second injections were given, consisting of 0.001 mg. If at the end of another forty-eight hours this produced no reaction, third tests using 0.01 mg. were made. By these tests it was planned to titrate the upper limit of sensitivity of the patients as indicated by the smallest amount of the tuberculin protein to which they would give a positive cutaneous reaction. After it became apparent that patients with Hodgkin's disease were never very sensitive to the protein, the smallest doses were omitted. There was no cause for regretting this because of any excessive reactions in subsequent patients.

This same antigen has been used in over two thousand persons—children and adults—in comparative tests with old tuberculin by Dr. Grace Hiller. She observed [16] that the human tuberculin protein used in test doses similar to those reported in this article gave results similar to those obtained by the use of old tuberculin in comparative amounts. Occasionally the response to the tuberculin protein was greater than to old tuberculin, but the reverse also occurred.

The smallest amount used in these tests, 0.0001 mg. of the tuberculin protein, is approximately equivalent to 0.1 cc. of a 1 : 10,000 dilution of old tuberculin. Similarly 0.001 mg. of tuberculin protein is approximately equivalent to a 1 : 1,000 dilution of old tuberculin and 0.01 mg. of tuberculin protein to a 1 : 100 dilution of old tuberculin.

The results are given in the accompanying table. No case was observed in any group in which a positive reaction to the avian and a negative reaction to the human tuberculin protein occurred. In practically every group cases were seen in which there were reactions to the

16. Hiller, Grace: Personal communication to the author.

human protein and no reaction whatever to the avian protein. Greater reactions to the avian tuberculin protein than to the human protein occurred in a few cases in several groups, but this was a less frequent finding than the reverse (i. e., a greater reaction with the human than with the avian protein).

A wholly unexpected observation was made. Early in the study the comparative absence of cutaneous reactions in the group with Hodgkin's disease as contrasted with the control cases was observed. It is true that the control groups were much smaller and that accurate deductions are impossible. But this trend was definite, and persisted throughout the experiments. In no instance was a positive cutaneous reaction to 0.0001 mg. of the proteins observed in a patient with Hodgkin's disease. Few tests were performed with this, the smallest dose, because with the

Cutaneous Reactions to Tuberculin Protein

		0.0001 Mg. (1:10,000)					0.001 Mg. (1:1,000)					0.01 Mg. (1:100)				
Diagnosis	Total No. Patients	Patients Tested	Both Negative	Av = Hu*	Av > Hu	Av < Hu	Patients Tested	Both Negative	Av = Hu	Av > Hu	Av < Hu	Patients Tested	Both Negative	Av = Hu	Av < Hu	Av > Hu
Hodgkin's disease	35	2	2	..	..	..	33	27	1	2	3	28	20	2	1	5
Leukemia	11	3	0	2	..	1	9	5	1	1	2	6	2	1	0	3
Lymphosarcoma	3	1	1	..	..	..	3	2	1	..	..	2	0	..	..	2
Carcinoma	6	0	..	..	..	..	6	2	..	..	4	1	0	..	..	1
Tuberculous adenitis	9	5	1	1	..	3	8	0	..	..	8	1	0	..	..	1
Nonspecific adenitis	9	2	0	2	..	..	8	3	..	..	5	2	0	1	1	..
Total	73															

* Av means avian and Hu, human tuberculin.

next larger dose of 0.001 mg. only six patients of thirty-three gave a reaction. In each of these six the reactions were very slight, so that a smaller test dose was not required to titrate the extent of the sensitivity. This is a large test dose for adults. However, when an even larger dose was used, namely, 0.01 mg. of the protein, twenty of twenty-eight patients tested failed to show sensitization. For adults this is an extremely large dose, and the failure of so many of the patients with Hodgkin's disease to react positively shows their extreme lack of sensitization. In the groups of cases other than Hodgkin's disease only a few patients were given this test dose because most of them had shown a reaction with smaller doses.

The statistical data fail to reveal several important observations. Although the reactions to the avian protein are occasionally charted as greater than those to the human protein, this difference was never very marked. On the other hand, there was occasionally a reaction to the human tuberculin-protein with an absence of reaction to the avian preparation.

The chart also fails to indicate the size of the reaction. In the patients with Hodgkin's disease who were sensitive to the test dose, the reaction was never large, and if the next larger test dose was given the response was not much greater. This behavior is unlike that of the sensitizations in most of the other groups. A patient with tuberculous adenitis who was barely sensitive to a certain test dose, if given the next larger dose, usually responded with a much greater reaction, even a maximal one with central necrosis.

In one case a "delayed reaction" was seen in a patient with Hodgkin's disease. There was no reaction to the first tests with 0.001 mg. when observed at forty-eight hours, so the largest dose of 0.01 mg. was then given. To this there was only a slight erythematous reaction in forty-eight hours. Three days later, however, a marked reaction was present at the sites of both tests. No similar reaction occurred in the other groups.

Repeated tests at intervals up to eight months were performed on some patients. Tests were also performed on a few patients before and after a series of roentgen treatments. No instance was noted in which a positive reaction occurred in a patient who had previously been insensitive. Neither did I see a reaction previously positive become negative.

COMMENT

It is generally recognized that if a large series of adults are given tuberculin tests with graded test doses, the largest of which is comparable in size to those used in the tests described, most of them give a positive reaction. This indicates sensitization to the tubercle bacillus or its products. The failure of patients with Hodgkin's disease to show this "normal" positive reaction can theoretically be explained in either of two ways. One possibility is that patients who acquire Hodgkin's disease are desensitized by the disease. If this is the correct explanation, this is the only chronic nontuberculous disease recognized at present that so regularly desensitizes its victims early while they are still in excellent general condition (certain tuberculous diseases of the skin are accompanied by an absence of cutaneous reaction to tuberculin[17]). The other possibility is that Hodgkin's disease occurs mainly in that small group of people in whom the "normal" adult sensitivity to tuberculin fails to develop. To prove this hypothesis it would be necessary to follow a large group of children to adult life with frequent tuberculin tests and observe whether Hodgkin's disease appeared only among those in whom a positive reaction never developed. In one patient in this series

17. Sulzberger, M. B.: Sarcoid of Boeck (Benign Miliary Lupoid) and Tuberculin Anergy, Am. Rev. Tuberc. **28**:734, 1933.

lesions of tuberculosis and of Hodgkin's disease were found in the same section of an excised lymph node. The patient was insensitive to tuberculin protein.

Regardless of which explanation is the correct one, it is difficult to conceive of this phenomenon occurring so regularly in a disease absolutely unrelated to tuberculosis. It cannot be attributed to the general condition of the patients because on the whole this was comparable in all groups. This failure of reaction was so marked that it was of value as presumptive evidence in diagnosis. It was of definite value in excluding tuberculous adenitis. It is offered as a valuable diagnostic procedure in the small group of patients who refuse biopsy and in whom it is advisable to exclude the possibility of active tuberculous adenitis before beginning treatment with large doses of roentgen rays.

The presence of a cutaneous reaction to the avian protein, found occasionally in each of the groups, must be explained. The experiments of Dolgopol [18] help explain this situation. She found that the presence of a positive reaction to avian tuberculin observed in many cases of pulmonary tuberculosis did not indicate an active or latent mixed infection of human and avian tubercle bacilli. She considered the positive reactions to avian tuberculin as a group reaction caused by sensitization with the mammalian types of tubercle bacilli. She stated that an infection by avian tubercle bacilli might be assumed to exist when the reaction to avian tuberculin was positive while the reaction to other tuberculins was negative or considerably weaker. The last two conditions were not seen during the experiments reported in this paper.

The results obtained with the tuberculin protein differ from those reported by Parker and his co-workers, which they obtained with old tuberculin. The results agree in that fewer positive reactions were found in patients with diseases of the lymphoid and myeloid tissues, including Hodgkin's disease, and with carcinoma than in tuberculous patients. They differ from Parker's results in that in this series (1) fewer positive reactions were found in Hodgkin's disease than in the other lymphomas and carcinomas as well as in tuberculosis, and (2) there were fewer positive reactions to avian tuberculin protein than to the human protein. This discrepancy is probably due to the difference in antigenic capacity of the test solutions used.

SUMMARY

Tuberculin protein (Seibert) was used in performing intracutaneous skin tests on thirty-five patients with Hodgkin's disease (lymphogranulomatosis) and on thirty-eight controls with a variety of lymphoma.

18. Dolgopol, V. B.: The Specificity of Avian Tuberculin Reactions, J. Infect. Dis. **49**:216 (Sept.) 1931.

Tuberculin proteins prepared from both avian and human strains were used in comparative tests for the purpose of obtaining information on the possible etiologic rôle of the avian tubercle bacillus in Hodgkin's disease.

No evidence of specific sensitization to the avian tuberculin protein was obtained in these tests. A marked desensitization (or absence of sensitization) was found to both proteins in the cases of Hodgkin's disease. This relative absence of "normal adult sensitization" was of diagnostic value, especially in the differential diagnosis of tuberculous adenitis. The incidence of absence of sensitization was greater in the group with Hodgkin's disease than in the groups of other lymphomas, which admittedly were small.

The interpretation was made either that (1) the process of Hodgkin's disease desensitizes its victims to these tuberculin proteins or that (2) Hodgkin's disease usually occurs in persons in whom development of the normal sensitization to the tuberculin protein is impossible.

It is difficult to conceive of either of these phenomena as occurring in a disease absolutely unrelated to tuberculosis.

CHRONIC SUPRARENAL INSUFFICIENCY

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In a recent article, we [1] reported a case of malnutritional edema which exhibited a unique clinical syndrome and a degenerative lesion of the suprarenal glands at autopsy. The outstanding clinical features of the syndrome were extreme emaciation with complete loss of body fat, asthenia, anorexia, polyneuritis, trophic ulcers, a high level of non-protein nitrogen in the blood, absence of pigmentation and hypotension. It was suggested that the syndrome was that of chronic suprarenal insufficiency, analogous to the similar state in animals produced by bilateral suprarenalectomy.

That chronic suprarenal insufficiency is not a rare condition is shown by the fact that we are now able to report three additional cases, two of which have come to autopsy. Interest has also been aroused in another aspect of the syndrome. One of us (M. P.) has called attention to the resemblance in the later stages between pellagra and chronic suprarenal insufficiency.[2] Recently Thannhauser [3] reported three cases of pellagra, in one of which an autopsy was performed by Aschoff.[4] Aside from the disappearance of the body fat and atrophy of the internal organs, the only significant lesion found was marked atrophy of the suprarenal cortex.

REPORT OF CASES

CASE 1.—G. S., an Italian, aged 53, was admitted to the Gouverneur Hospital on Dec. 11, 1932. The history, obtained through relatives, was that two months before admission he had eaten a condemned chicken and had since become progressively weaker. He had complained of anorexia and pains in the right thigh and in the costolumbar region.

Physical examination revealed a markedly cachectic, irrational, middle-aged man. Both lower extremities and the sacrum were moderately edematous. There

1. Packard, M., and Wechsler, H. F.: Chronic Adrenal Insufficiency, Am. J. M. Sc. **186**:66, 1933.

2. Packard, M.: Discussion at Symposium on the Suprarenal Glands before the Section of Medicine, New York Academy of Medicine, Jan. 17, 1933.

3. Thannhauser, S. J.: Pellagra und Endocrine Störungen, München. med. Wchnschr. **80**:291, 1933.

4. Aschoff, L.: Pathologische-anatomische Bemerkungen zu dem vorausgehenden Aufsatz, München. med. Wchnschr. **80**:296, 1933.

was no pigmentation of the skin or visible mucous membranes. A prolonged Sergent white line was elicited. The pupils were dilated but reacted to light. There was bilateral ptosis of the eyelids. The fundi were normal. The breath was foul, the tongue was slightly coated and tremulous, and the teeth were carious.

The lungs were normal. The apex beat of the heart was in the fourth interspace, 7 cm. from the midsternal line. The sounds were of poor quality, but no murmurs were audible. The pulses were equal, regular and soft, and the pulse rate was 80. The blood pressure was 110 systolic and 70 diastolic. The abdomen was normal.

Quadriparesis, more marked in the lower extremities, was demonstrable. All the deep reflexes were absent with the exception of the finger jerks and the left knee jerk. The left abdominal reflex could not be elicited. The plantar reflexes were normal.

Laboratory Examination.—The blood count revealed: red cells, 4,750,000; hemoglobin, 66 per cent (Sahli); white blood cells, 5,000; neutrophils, 66 per cent; lymphocytes, 30 per cent, and mononuclears, 4 per cent. The urine had a specific gravity of 1.020, gave an acid reaction and showed no sugar but a trace of albumin, a few leukocytes and an occasional red blood cell. After sodium thiosulphate was administered intravenously the urine contained 0.005 mg. of arsenic and traces of lead. The Wassermann reaction of the blood was negative. The cerebrospinal fluid was clear and under normal pressure. It contained no globulin or sugar, and there were 16 cells per cubic millimeter. The Wassermann reaction and the colloidal gold tests were negative. Chemical examination of the blood plasma showed: nonprotein nitrogen, 38 mg., and sugar, 100 mg.

Course.—The course was progressively and rapidly downward. The loss of subcutaneous fat became more pronounced, but the skin retained its elasticity. A large bedsore quickly developed on the right buttock. The patient remained irrational and became very tremulous; involuntary athetoid movements in the upper extremities appeared. Five days after admission, signs of bronchopneumonia were evident, and the temperature rose steadily, reaching 106.6 F. at the time of death on the seventh day.

Autopsy.—The anatomic findings were: cachexia with extreme loss of adipose tissue and atrophy of the internal organs; decubitus ulcer on the right buttock; chronic adhesive pleuritis; bronchopneumonia; dilatation of the right side of the heart; chronic perihepatitis and perisplenitis; congestion of the liver; chronic splenitis; petechial hemorrhages of the mesentery; idiopathic atrophy of the right suprarenal gland, and hypertrophy and degeneration of the left suprarenal gland.

The only vestige of the right suprarenal gland was a small piece of dark brown tissue, 8 mm. in length. Histologic study of the sections revealed a thick capsule of fibrous tissue enclosing an extremely narrowed and distorted cortex. The cortex consisted for the most part of islands of greatly altered cortical cells separated by thick bands of hyaline fibrous tissue. Occasionally isolated cortical cells were found. Most of the cells were large with poorly staining, vacuolated cytoplasm and deeply staining, irregular nuclei. Other cells were deeply pigmented, and exhibited varying stages of necrosis. Between the cortical islands, and occasionally between the individual cells, were numerous lymphocytes and an occasional plasma cell. The medulla, although greatly reduced in size, was apparently normal.

The left suprarenal gland was enlarged, weighing 12.8 Gm., and on section had a grayish, homogeneous appearance. Microscopically the cortex was the seat of moderately advanced vacuolar degeneration, most marked in the inner layer of

the zona fasciculata and in the zona reticulata. The cortical cells in these areas were hyperplastic, and the cytoplasm was vacuolated. Necrosis was slight. The stroma was edematous and congested, contained a few small hemorrhages, and was scantily infiltrated with round cells. In the zona reticulata capillary and small venous thromboses were present. The medulla showed no changes.

Comment.—The diagnosis of malnutritional edema is complicated in this case by the possibility of some form of poisoning. However, the absence of gastro-intestinal and renal symptoms, the negative observations with regard to these organs at autopsy and the quantitative analysis of the urine for heavy metals make this seem unlikely. The clinical syndrome is practically the exact counterpart of the case of chronic suprarenal insufficiency previously reported. The shorter course of the illness explains the fact that although the body fat was tremendously reduced, it had not entirely disappeared. The suprarenal lesion not only is of interest but probably accounts for the shorter duration of the disease. The pathologic changes in the right suprarenal gland are typical of those described in idiopathic suprarenal atrophy; the condition was obviously an old process. The cause of idiopathic suprarenal atrophy is unknown; when bilateral, it is usually accompanied by the symptoms of Addison's disease. The degenerative changes in the left suprarenal gland are similar to but less marked than those in our first case of malnutritional edema. As there was but one adequately functioning suprarenal gland, a moderate degeneration of this gland produced the syndrome of chronic suprarenal insufficiency.

Case 2.—F. S., an Austrian, aged 68, was admitted to the hospital on May 26, 1933, complaining of dyspnea, anorexia and pain in the right side of the chest. In 1925, after repair of a bilateral inguinal hernia, a cough developed. Roentgenograms of the chest, taken at that time, showed an enlarged heart and healed tuberculous lesions at both apexes. Since the operation the patient had suffered from constricting pains in the chest on exertion. For the past year he had had severe pains and stiffness in the joints of both hands, which had been treated with injections and by extraction of the teeth. For the past six weeks he had complained of increasing dyspnea on exertion and of occasional shooting pains in the right side of the chest. These pains were now continuous, and radiated down to the costal margin and around to the back. The loss of appetite was marked, and constipation was present. A frequent cough, productive of thick, whitish sputum, had developed recently. Nocturia was present.

Physical examination revealed a markedly undernourished, dyspneic, cyanotic, elderly man. In spite of emaciation the skin retained its elasticity. There was no pigmentation, and Sergent's white line was prolonged.

The pupils were equal and reacted to light and in accommodation. The eyegrounds showed moderate angiosclerosis. The tongue was coated, and the pharynx was slightly reddened. All the teeth were absent except two lower canines supporting a plate.

There was dulness to flatness over the entire lower right side of the chest, with absence of fremitus and breath sounds over this area. Slightly increased breath sounds and occasional moist râles were present above the area of dulness. The left side of the chest was hyperresonant.

The borders of the heart could not be determined accurately. The first sound at the apex was distant, of poor quality and totally irregular. A soft systolic murmur was audible over the aortic area which became intensified over the upper end of the sternum and in the neck. The pulses were equal and totally irregular, with a rate of 72, and the radial walls were thickened. There was no pulse deficit. The blood pressure was 140 systolic and 55 diastolic.

The abdomen was soft and showed the old hernial incisions. The liver was palpable two fingerbreadths below the costal arch. The lower pole of the right kidney was palpable. The right scrotal sac was filled with fluid. There were a few external tabs about the anus. The prostate gland was not enlarged, and no masses were felt.

Marked clubbing of the fingers and atrophic arthritic changes in the metacarpophalangeal and the proximal interphalangeal joints were present. There was no edema.

Laboratory Examination.—The blood count showed: red cells, 4,740,000; hemoglobin, 80 per cent; white cells, 12,800; neutrophils, 84 per cent; lymphocytes, 14 per cent, and eosinophils, 2 per cent. Examination of the urine revealed: albumin, 2 plus, and occasional hyaline and granular casts. The Wassermann reaction of the blood was negative. Chemical examination of the blood plasma showed: urea nitrogen, 15.6 mg., and sugar, 74 mg. Tests of the sputum were repeatedly negative for tubercle bacilli.

An electrocardiogram showed auricular fibrillation and diffuse myocardial degeneration.

Roentgenograms of the chest revealed a thickened pleura and an effusion at the base on the right side and an enlarged heart. After the removal of the fluid and artificial pneumothorax the lower lobe of the right lung was collapsed; at the tip was a nodular elevation which suggested a malignant process. Proctoscopy and a barium sulphate clysma gave negative results.

The fluid removed from the effusion was straw-colored, and contained 1,810 white blood cells per cubic millimeter, with 20 per cent neutrophils and 80 per cent lymphocytes. The fluid was sterile on culture, and revealed no tumor cells.

Course.—The patient suffered from extreme anorexia and asthenia, which were not improved by the administration of insulin and dextrose. The emaciation was progressive, and the loss of body fat was complete. A large bedsore developed over the sacrum. He complained of pains in the arms and legs, and the muscles and nerves of the extremities were extremely tender. The superficial and deep reflexes progressively diminished and finally disappeared. He became increasingly apathetic and tremulous. The blood pressure was stationary, and the signs in the chest were unaltered except for an increase in the effusion. On July 12, the urea nitrogen was 32 mg. The course was afebrile with the exception of two days in June, when, owing to impacted feces, there was a moderate fever. On July 5, the temperature rose to 102 F., and the fever continued irregularly to July 23, when the patient died. The temperature on the day of death was 99 F. He was irrational during the last week of the illness.

Autopsy.—The anatomic diagnosis was: decubitus ulcer of the sacrum; chronic adhesive pleuritis; hydrothorax on the right side; scirrhous adenocarcinoma of the right hyparterial bronchus with stenosis of the lumen; suppurative bronchopneumonia and chronic interstitial pneumonitis of the lower lobe of the right lung; emphysema of the left lung; healed apical tuberculosis; dilatation of the right side of the heart; advanced atherosclerosis of the aorta and coronary arteries; organ-

ized thromboses of the descending branch of the left coronary and of the right circumflex arteries; chronic myocardosis; a healed infarction of the lower two thirds of the left ventricle and the interventricular septum, with an early aneurysmal formation; chronic passive congestion and parenchymatous and fatty degeneration of the liver; chronic perisplenitis; acute and chronic splenitis; arteriosclerotic nephritis; prostatic hypertrophy, and carcinomatous metastases to both suprarenal glands, the paravertebral lymph nodes and the right kidney.

The right suprarenal gland was enlarged to about the size of a woman's fist. On section it was entirely replaced by grayish-pink, homogeneous tumor tissue except for a thin rim in one area in which suprarenal tissue was still recognizable. The left suprarenal gland was somewhat larger and firmer than normal, and on section a nodule of tumor tissue was found at one pole. Microscopic examination of the right suprarenal gland showed the tumor to be an adenocarcinoma of the same structure as the carcinoma of the bronchus. Only a narrow rim of degenerating and necrotic suprarenal tissue remained. The left suprarenal gland exhibited, besides the tumor metastasis, marked vacuolar degeneration of the cortical cells and numerous small hemorrhages in the zona fasciculata.

Comment.—The case exhibits all the classic features of chronic suprarenal insufficiency. There was no pigmentation, and the blood pressure was stationary throughout the illness, in spite of an old coronary occlusion and advanced myocardosis. The bronchial carcinoma was productive of many of the symptoms and in all probability played a rôle in the cachexia, but it could not conceivably produce the syndrome which is so exactly the counterpart of that occasioned by malnutrition. Miller and Jones,[5] in a review of eight hundred and eight cases of carcinoma of the lung, found metastases to the suprarenal glands in 9.7 per cent of the cases. The complete replacement of one suprarenal gland and the partial involvement of the other by metastases furnish an adequate pathologic basis for the clinical picture.

CASE 3.—B., a Jewish woman, aged 39, came under observation on Aug. 23, 1933. Her chief complaints were weakness and loss of weight. Nine years before, she began to suffer from "gas pains" and periodic attacks of nausea and vomiting. The vomitus would consist at first of food eaten and then of bile. Blood was never present. Roentgenograms of the gastro-intestinal tract were negative, and a diagnosis of gastric neurosis was made by several clinicians. The patient was placed on a restricted diet, especially in regard to vegetables, which the patient further reduced of her own accord. During the past year, she had had marked anorexia and four or five loose bowel movements daily without evident steatorrhea, and had lost 52 pounds (23.6 Kg.). Her weight at the commencement of the illness was 150 pounds (68 Kg.). She complained of extreme exhaustion and pain, stiffness, weakness and loss of power in all the extremities. Her former jovial disposition had changed to one of anxiety and apprehension, and she felt constantly depressed. Sexual desire was completely absent, and amenorrhea had been present for the past three months. A son had been asthmatic since birth, and was allergic to a number of foods.

5. Miller, J. A., and Jones, O. R.: Primary Carcinoma of the Lung, Am. Rev. Tuberc. **21**:1, 1930.

Physical examination revealed a short, thin woman, who looked chronically ill. There was a complete loss of subcutaneous fat. The height was 59 inches (150 cm.) and the weight 72 pounds (32.7 Kg.). Freckles were present on the face, arms, abdomen and legs. There was no pigmentation of the visible mucous membranes. Sergent's white line was present. The pupils were equal and regular and reacted to light and in accommodation. The thyroid gland was not palpable. The lungs were clear, and the heart was normal. The pulse was regular and soft with a rate of 68. The blood pressure was 78 systolic and 60 diastolic. There were no pathologic findings in the abdomen, but costovertebral tenderness was elicited. The knee jerks were sluggish, but there were no abnormal reflexes. Several anesthetic areas could be mapped out on the legs.

Laboratory Examination.—The blood count revealed: red cells, 4,400,000; hemoglobin, 85 per cent, and white cells, 9,000, normal differential count. The urine was essentially normal. Chemical examination of the blood plasma showed: urea nitrogen, 32 mg.; sugar, 112 mg., and creatinine, 1 mg. The Wassermann reaction of the blood was negative. The basal metabolic rate was minus 5 per cent. According to a test meal Ewald's technic showed moderate subacidity. Roentgenograms of the chest showed no signs of tuberculosis.

The patient is receiving treatment, which includes injections of a proprietary preparation of the cortical hormone three times a week and a diet high in vitamin B. In the short time she has been under observation, the patient has made considerable progress. She has gained 8 pounds (3.6 Kg.), and the blood pressure is now 100 systolic and 75 diastolic.

Comment.—This case could be classified as atypical Addison's disease. However, the complete loss of subcutaneous fat, the polyneuritis, the absence of pigmentation and tuberculosis and the history of malnutrition have led us to include it under the syndrome of chronic suprarenal insufficiency. The hypotension is difficult to explain except that this was our only case in a woman and, in all probability, in a hypotensive person. The encouraging response to treatment with extracts of the suprarenal cortex is of interest.

GENERAL COMMENT

Etiology.—Three of the patients were men and one a woman. The respective ages were 50, 53, 68 and 39 years. Malnutrition was the apparent etiologic factor in three. As the hypertrophy and degeneration of the suprarenal glands in inanition and the various vitamin deficiencies have been commented on elsewhere, they need not be reviewed here. In one case the suprarenal glands were involved by a metastatic carcinoma. Addison[6] recognized three causes of the disease which bears his name: tuberculosis, atrophy and carcinoma. Four of his eleven patients with the disease had malignant growths of the suprarenal glands. The clinical reports, however, are incomplete or lacking, and

6. Addison, T.: A Collection of the Published Writings of the late Thomas Addison, London, The New Sydenham Society, 1868.

Wilks [7] rejected these cases as true examples of the disease. Since that time the question as to whether carcinoma can cause the disease has been in dispute. The evidence against this assumption has been steadily accumulating with the advance in clinical and pathologic knowledge. In the older compilations of reported cases, such as Lewin's,[8] a few are listed in this classification. The clinical and pathologic descriptions of these cases, however, are not convincing. Some cannot be considered as true Addison's disease, according to modern criteria, while in others the actual presence of a malignant tumor is doubtful. In all the recent large collections of reports of Addison's disease, verified by necropsy, such as those of Conybeare and Millis [9] and Rowntree and Snell,[10] carcinoma has not been found in a single instance. Addison [6] was aware of the fact that malignant disease might exist in and partially or completely destroy both capsules without the appearance of pigmentation. The literature contains reports of many such cases. Rowntree and Snell [10] stated that in seventy cases in which one or both glands were carcinomatous the clinical picture was not typical of Addison's disease. It is interesting to conjecture how many of these would fit into the syndrome of chronic suprarenal insufficiency. Additional evidence that a malignant process can produce such a clinical picture is furnished by the primary tumors of the suprarenal cortex. In contrast to the usual obesity, cases are occasionally encountered in which extreme emaciation and loss of practically all the fat are seen.[11] It would seem that this is due to destruction of the suprarenal tissue, as the other symptoms of suprarenal hyperactivity are not so pronounced or are absent altogether.

Pathology.—There were two significant findings at autopsy: an extreme to complete loss of body fat, accompanied by atrophy of the internal organs and a suprarenal lesion. The loss of fat was striking, involving not only the panniculus adiposus but also the internal fat depots. In the cases associated with malnutrition the suprarenal lesion was one of hypertrophy and degeneration. The latter change was evidenced by vacuolar degeneration of the cortical cells, with areas of necrosis and regeneration, and hyperemia, edema, hemorrhages and

7. Wilks, S.: On Disease of the Suprarenal Capsules; or Morbus Addisonii, Guy's Hosp. Rep. **1**:63, 1862.

8. Lewin, G.: Ueber Morbus Addisonii, Charité-Ann. **17**:536, 1891.

9. Conybear, J. J., and Millis, G. C.: Observations on Twenty-nine Cases of Addison's Disease Treated in Guy's Hospital Between 1904 and 1923, Guy's Hosp. Rep. **74**: 369, 1924.

10. Rowntree, L. G., and Snell, A. M.: A Clinical Study of Addison's Disease, Philadelphia, W. B. Saunders Company, 1931.

11. Cecil, H. L.: Hypertension, Obesity, Virilism and Pseudohermaphroditism as Caused by Suprarenal Tumors, J.A.M.A. **100**:463 (Feb. 18) 1933.

capillary and venous thromboses of the interstitial tissue. What may have served as a contributory factor in one of the cases was the practically complete destruction of the right suprarenal capsule by idiopathic suprarenal atrophy.

Clinical Considerations.—The early symptoms of the disease are profound anorexia, marked weakness, apathy and progressive loss in weight. There is no pigmentation of the skin or visible mucous membranes. A prolonged Sergent white line can be elicited. The wasting is extreme, and can continue until there is a complete loss of the body fat; the skin, however, retains its elasticity. The aversion to food is continuous and is not limited to any particular type; it is not accompanied by nausea, retching or vomiting. The disposition alters completely, the patient becoming increasingly morose, lethargic and desirous of death. Pains, paresthesias and weakness in the extremities develop, and the signs of polyneuritis, such as tenderness of the nerve trunks, diminution or absence of reflexes, areas of anesthesia and paresis of the limbs, become manifest. Trophic ulcers also make their appearance in spite of every precaution. The patient becomes delirious, and tremulous and athetoid movements are noted. Death is due to bronchopneumonia. The course is afebrile except for the onset of the terminal illness, and the final temperature is usually subnormal. Hypotension was lacking in the three cases verified by necropsy. In the woman now under observation the systolic blood pressure was only 78. Just as typical Addison's disease, in patients with coexisting essential hypertension, may occasionally be associated with high blood pressure, the low blood pressure in this case can best be explained by the occurrence of the syndrome in a hypotensive person.

Laboratory Findings.—The only significant finding is moderately increased nonprotein nitrogen in the blood. Moderate secondary anemia is present.

Differential Diagnosis.—The only disease that must be seriously considered in the differential diagnosis is Addison's disease. In 1855 Addison epitomized its signs and symptoms as follows: "The leading and characteristic features of the morbid state to which I would direct attention are anemia, general languor and debility, remarkable flabbiness of the heart's action, irritability of the stomach and a peculiar change of colour of the skin, occurring in connection with a diseased condition of the suprarenal capsules." In the three quarters of a century that has elapsed since then, little of importance has been added to this description. Addison's inclusion of anemia as a major symptom of the disease has been shown to be partially incorrect. There is rather a deficient circulation and utilization of oxygen, and, in the crises, a marked diminution in the volume of the blood is noted. The latter is associated

with a rise in the nonprotein nitrogen values of the blood. Hypotension has been added as a cardinal sign, and the frequent loss of weight and the occurrence of subnormal temperature have been emphasized by many clinicians. As would be expected in a syndrome based on diseased suprarenal capsules, chronic suprarenal insufficiency closely resembles this malady. The absence of many of the cardinal features, especially pigmentation and hypotension, plus the appearance of additional factors such as the practically complete loss of body fat, polyneuritis and trophic ulcers sufficiently differentiate the two conditions. So-called atypical cases of Addison's disease are not uncommon, and it is for future observation to decide whether many of these do not rightly belong under the classification of chronic suprarenal insufficiency, particularly those based on malnutrition or carcinoma.

Pituitary cachexia offers little difficulty in the differential diagnosis, as the disease runs an exquisitely chronic course, and the emaciation is accompanied by wrinkling of the skin, falling out of the hair and teeth and atrophy of the genitalia. In multiple sclerosis of the endocrine glands, symptoms of both myxedema and suprarenal insufficiency are added to those of pituitary cachexia.

Treatment.—In only one case has specific therapy been attempted. With the use of a proprietary preparation of the cortical hormone and a diet high in vitamin B, encouraging results are being obtained.

SUMMARY

Three additional cases of chronic suprarenal insufficiency are reported, and the entire group is analyzed. The etiology, pathology, symptoms, differential diagnosis and treatment are discussed.

CHRONIC ARTHRITIS

SEROLOGIC AND CLINICAL STUDIES

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The present investigation was initiated to establish a better understanding of the serology of chronic arthritis and, more particularly, the arthritis that has been considered infectious. Our interest centered on four major topics: (1) the specificity and sensitivity of the streptococcic agglutination reaction in chronic infectious arthritis, as reported by Cecil, Nicholls and Stainsby [1] and confirmed by Dawson, Olmstead and Boots; [2] (2) the relation between agglutinin titer and cutaneous sensitivity; (3) the relation between agglutinin titer and clinical course, and (4) the effect of vaccine treatment on agglutinin titer.

Organisms of four types commonly isolated by our laboratory from foci of infection in patients with chronic arthritis were selected for this study. In addition, we chose members of three bacterial groups which are frequently implicated, according to the reports of leading authorities on the disease.

SELECTION OF ORGANISMS

The following brief résumé of the literature serves to indicate the diversity of current opinion regarding the organisms involved in arthritis and the organisms recommended for vaccine therapy. During the last fifteen years, many clinicians and bacteriologists have attempted to isolate the causal factor in cases of arthritis, using as source material blood, fluid and tissues from the affected joints and secretions and excretions from other loci as numerous as the parts of the human body. The organisms isolated are of many different genera. Those most often reported are, in order of frequency: streptococci of the hemolytic, viridans and anhemolytic types, diplococci, diphtheroids, staphylococci, intestinal organisms of the colon-typhoid group, gonococci, pneumococci

From the Desert Sanatorium and Institute of Research.

1. Cecil, R. L.; Nicholls, E. E., and Stainsby, W. J.: Bacteriology of Blood and Joints in Chronic Infectious Arthritis, Arch. Int. Med. **43**:571 (May) 1929; J. Exper. Med. **50**:617, 1929; Am. J. M. Sc. **181**:12, 1931.

2. (*a*) Dawson, M. H.; Olmstead, M., and Boots, R. H.: Proc. Soc. Exper. Biol. & Med. **28**:419, 1931; (*b*) ibid. **28**:421, 1931; (*c*) J. Immunol. **23**:187, 1932; (*d*) ibid. **23**:205, 1932.

and even anaerobes of the Clostridium Welchii group. An exhaustive summary of the bacteriologic observations in atrophic arthritis may be found in the *Annals of the Pickett-Thomson Research Laboratory,*[3] and the critical reviews of the subject by Jordan and Vrtiak and Jordan [4] and by Miller [5] are complete. The reader is also referred to "A Symposium on Arthritis." [6]

Recently stress has been laid on the streptococci by the reports of Cecil and his associates [1] that they have isolated with considerable regularity from the blood and joints of patients with atrophic arthritis a strain of Streptococcus haemolyticus which is of a constant cultural character, agglutinates readily with the serums of patients with atrophic arthritis and produces a disease similar to atrophic arthritis when injected intravenously into rabbits; it has been chosen by Cecil as a therapeutic agent in the form of vaccine in selected cases. Dawson, Olmstead and Boots were unable to isolate a significant organism from cultures of the blood, joints or nodules in a series of 80 patients with arthritis.[2a] They found, however, that Cecil's typical hemolytic streptococcus is agglutinated by serums from patients with atrophic arthritis in the great majority of cases to a high titer, and that other hemolytic streptococci of the scarlatinae-erysipelatis group agglutinate equally well.[7] They found no evidence of a specific reaction which could differentiate any of the hemolytic strains examined. Burbank and Hadjopoulos,[8] following Hastings,[9] are strong proponents of the complement-fixation reaction as an aid in the diagnosis and treatment of arthritis. They reported that serums from patients with atrophic arthritis bind complement with certain stock and autogenous hemolytic streptococci which they isolated from the blood, feces, urine or local lesions (in teeth, tonsils and other localities) of patients with atrophic arthritis. In addition, they stated that a patient is often improved by treatment with a vaccine made from the streptococci which show fixation with his serum. They recently published the results of experiments in which rabbits artificially infected with hemolytic or green-producing streptococci cul-

3. Thomson, D., and Thomson, R.: The Pathogenic Streptococci, Ann. Pickett-Thomson Research Lab., 1929, vol. 4, pts. 1 and 2.

4. Jordan, E. P.: Microbic Etiology of Rheumatic Fever and Arthritis, Arch. Path. **10**:79 (July) 1930. Vrtiak, E. G., and Jordan, E. P.: Clinical Study of Chronic Arthritis, J. A. M. A. **94**:863 (March 22) 1930.

5. Miller, J. L.: Am. J. M. Sc. **182**:158, 1931.

6. Symposium on Arthritis, J. Lab. & Clin. Med. **15**:1055 (Aug.); 177 (Sept.) 1930.

7. Dawson, Olmstead and Boots (footnote 2 *b*, *c* and *d*).

8. Burbank, R., and Hadjopoulos, L. G.: Serologic Significance of Streptococci in Arthritis and Allied Conditions, J. A. M. A. **84**:637 (Feb. 28) 1925; J. Lab. & Clin. Med. **14**:131, 1928.

9. Hastings, T. W.: J. Exper. Med. **20**:52, 1914.

tured from the blood of patients with arthritis manifested the typical symptoms and pathologic changes of arthritis; the injected organisms could regularly be recovered from the animals' joints and could be demonstrated within the synovial tissues and bone tissues of the affected parts.[10] Some of the arthrotropic streptococci isolated by Crowe [11] have been compared with the strains of Burbank and are said to be similar or identical.[12] Attempts to culture significant bacteria from the blood of arthritic patients by the method of Cecil, Nicholls and Stainsby [1] have failed in our laboratory.[13]

MATERIALS AND TECHNIC

History and Characteristics of Cultures.—Originally 7 organisms were selected. They included Cecil's typical arthrotropic hemolytic streptococcus strain AB 13,[14] the NY 5 strain of Str. scarlatinae,[15] Cecil's anhemolytic streptococcus RB 5 [14] and 4 organisms isolated from patients in the Desert Sanatorium; the hemolytic streptococcus W and Bacterium coli H were isolated repeatedly by us from the fresh stools of 2 patients in far advanced stages of atrophic arthritis; Str. viridans M was isolated from the throat and repeatedly in almost pure culture from the rectal mucosa of a young man with a long history and advanced symptoms of spondylitis. Staphylococcus aureus P was for more than a year the characteristic organism in the nasal discharge in a severe case of chronic sinusitis (nonarthritic). In addition to the 7 organisms listed, several other streptococci which had been isolated from cases of atrophic arthritis in representative laboratories were employed during the preliminary work, but were discarded because of their failure to produce significant serologic or cutaneous reactions. Str. haemolyticus NY 5 was abandoned early, since it gave evidence of a biochemical and serologic relationship to AB 13, always reacting with serums which agglutinated Cecil's organism, but always in lesser degree. The cultural characteristics of the remaining streptococci are shown in table 1. They remained constant, with the exception of Str. viridans M, which of late has tended toward the hemolytic type. Bact. coli H is of the communis variety and is an active hemolyzer; Staph. aureus P is typical in the production of pigment and occasionally hemolyzes blood agar.

Agglutinating serums for each of these streptococci were prepared by repeatedly inoculating rabbits with killed and live young organisms. Injections were made on four consecutive days each week for from six to twelve weeks, beginning with minimal doses and reaching a maximal approximate dose of from 5,000,000,000 to 10,000,000,000 organisms. With this technic, no agglutinin titers above 1,280 were obtained. Absorption of agglutinins in these serums by the 4 streptococci indicated that Str. haemolyticus AB 13 and Str. haemolyticus W were separate serologic entities. Absorption of AB 13 serum by the heterologous organisms did not greatly diminish AB 13 agglutinins. Str. haemolyticus W differed from the

10. Hadjopoulos, L. G., and Burbank, R.: J. Bone & Joint Surg. **14**:471, 1932.

11. Crowe, Warren: Ann. Pickett-Thomson Research Lab. **4**:398, 1929.

12. Thompson, David: J. Lab. & Clin. Med. **11**:1117, 1931.

13. Mote, J.: Unpublished communication to the authors.

14. These organisms were obtained through Dr. Stainsby; they were isolated in his laboratory from patients with atrophic arthritis and rheumatic fever, respectively.

15. This organism was isolated by Dr. Dochez from the throat of a patient with scarlet fever and obtained through Dr. Boots' laboratory.

other streptococci in that it was repeatedly pathogenic for rabbits, killing them regularly within three or four days with evidence of septicemia and renal involvement when doses of approximately from 1,000,000,000 to 5,000,000,000 organisms were given. No other streptococcus tested was lethal for rabbits in the doses given.

All of the organisms used in agglutination tests were from fresh live broth cultures. The streptococci were transferred at one or two day intervals to beef heart broth p_H 7.6, prepared according to the technic of Nicholls and Stainsby,[16] to which was added fresh citrated rabbit blood, 5 per cent by volume. Antigen flasks containing 80 cc. of beef heart broth were inoculated from "starter" blood-broth cultures of streptococci which were in the initial period of logarithmic growth (from five to six hour cultures) and were incubated for twenty-four hours before use. We soon discovered that more vigorously growing, diffuse and stable

TABLE 1.—*Cultural Characteristics of Streptococci Used in Agglutination and Skin Tests as a Routine*

Organisms	Morphology of Organisms	Morphology of Colony	Zone on Blood Agar	Sugar Fermentation		Milk
				Mannite	Inulin	
Str. haemolyticus AB 13	Long chains; cocci round, varying markedly in size in same chain	Finely granular, small, undulant; intermediate SR	Narrow zone of incomplete hemolysis	—	—	A
Str. haemolyticus W	Short chains; cocci large, often lance-shaped	Large, mucoid, dewdrop, smooth	Wide zone of vigorous hemolysis	+	+	A
Str. viridans M	Short chains; cocci round and lance-shaped	Pinpoint, flat, round, smooth	Good production of methemoglobin	—	+	C++
Str. anhaemolyticus RB 5	Long chains; cocci usually round; occasional bacillary forms		Indefinite production of methemoglobin	—	+	A C+

All of the streptococci produced acid without gas in dextrose, lactose, sucrose and salicin; all were bile-insoluble and did not liquefy gelatin.

Acid formation and no gas are denoted by +; no acid formation and no gas, by —; acid formation and no clot, by A; acid formation and hard clot, by AC, and extensiveness of clotting by C+ or C++.

antigens could be obtained in the following manner: The broth was buffered with 5 per cent dibasic potassium phosphate, and 1 per cent dextrose was added at the time of inoculation; after the supernatant homogeneous suspension was incubated for not more than twenty hours it was decanted and the reaction readjusted with double normal sodium hydroxide to p_H 7.6. Occasionally the streptococci agglutinated spontaneously even with these precautions, but this difficulty was generally overcome by rapid transfer twice a day in blood broth for from six to ten days. Satisfactory staphylococcus and Bact. coli agglutinogens were readily prepared in ordinary veal infusion broth, p_H 7.4, which was incubated from eighteen to twenty-four hours.

Antigens for skin testing and vaccine therapy were made from organisms grown as for agglutination, concentrated by centrifugation, washed four times in 5 per cent phenol-saline and resuspended to a standard density in phenol-saline solution. After standardization by direct count and sterility tests, the antigens were released for clinical use.

16. Nicholls, E. E., and Stainsby, W. J.: J. Clin. Investigation **10**:323, 1931.

Technic.—Serums for agglutination tests were collected by one of us from arthritic and control groups and sent under serial number to the laboratory. After the first short series, scrupulous care was taken that the clinician and the serologist should not know each other's results until the tests were completed. Final concentrations of the serum after the addition of antigen ranged from 1:40 to 1:2,560, as a routine; the final volume per tube was 1 cc. Tests were incubated in a constant-level water bath at 56 C. for two hours, then refrigerated overnight and read approximately eighteen hours after being set up. Readings immediately after incubation in a water bath were not sufficiently definite, owing to the slow formation of readily visible aggregates. All readings were made by one observer with the naked eye, then checked with a magnifying double-prism optician's loupe. The highest dilution in which definite, well formed clumps of micro-organisms could be seen was considered the serum titer.

RESULTS

In analyzing our data on patients with arthritis it seemed advisable to us to use the system of clinical grouping which was developed by Dr. Holbrook [17] in the Desert Sanatorium and Institute of Research and which has proved to be practical and helpful to us in selecting therapeutic measures. We present the following brief summary of his classification, in which atrophic arthritis is divided into two groups. Group 1 is an afebrile, insidious, progressive, symmetrical deforming and crippling disease. Group 2 is a febrile disease, often acute in onset, with heat, redness and swelling of the joints. Group 3 is commonly designated as osteo-arthritis, hypertrophic arthritis or degenerative arthritis. Group 4 A is spondylitis without bony ankylosis. Group 4 B is spondylitis with bony ankylosis. Group 5 is often termed metabolic, traumatic or menopausal arthritis, ordinarily with involvement of only one joint. Group 6 may properly be termed prearthritis, and in it are included all of the manifestations of neuritis, myositis, bursitis, fibrositis and similar conditions.

Sixty-seven cases of arthritis (all forms) fell readily into definite clinical groups. From these a total of 259 specimens were collected and tested for agglutinins against the 6 selected type organisms. The control group comprised 119 patients, from whom 174 specimens were collected. It will be seen from tables 2 and 3 that Cecil's hemolytic streptococcus AB 13 reacted in high serum dilution with 70 per cent of the serum specimens of types I and II, and with the specimens from about 75 per cent of the cases in these groups. This is a markedly higher frequency than was demonstrable with any of the other antigens. In no other clinical group was the percentage of high AB 13 titers so remarkable, the only runners-up being group 4 A, which may be atrophic arthritis of the spine, and the group of rheumatic infections. Except in cases of atrophic arthritis, the agglutinins against AB 13 are infre-

17. Holbrook, W. P.: Southwestern Med. **16**:149, 1932.

TABLE 2.—*Percentages of Clinically Grouped Specimens Which Agglutinate with Selected Micro-Organisms*

Clinical Diagnosis	Str. Haemolyticus AB 13			Str. Haemolyticus W			Str. Viridans M			Str. Anhaemolyticus RB 5			Staph. Aureus P			Bact. Coli H		
	Total Specimens	+320 or Over	All +	Total Specimens	+320 or Over	All +	Total Specimens	+320 or Over	All +	Total Specimens	+320 or Over	All +	Total Specimens	+320 or Over	All +	Total Specimens	+320 or Over	All +
Arthritic Groups:																		
Type I	59	71	88	59	8	44	59	19	61	58	33	69	59	5	54	58	12	26
Type II	138	70	90	135	13	45	133	9	61	133	49	84	135	4	42	128	8	30
Type III	13	8	31	11	9	18	11	0	9	11	18	64	11	0	9	9	(1)	(1)
Type IV A	37	43	65	35	50	75	36	3	42	36	25	89	36	3	25	36	3	11
Type IV B	6	(0)	(1)	5	(1)	(2)	5	(0)	(0)	5	(0)	(2)	5	(0)	(0)	4	(0)	(0)
Type V	6	(0)	(2)	5	(0)	(2)	3	(0)	(0)	5	(2)	(5)	4	(0)	(1)	3	(0)	(0)
Control Groups:																		
Normal	49	0	2	6	(2)	(5)	6	(0)	(1)	6	(2)	(4)	6	(0)	(1)	6	(0)	(0)
Tuberculosis	23	0	4	3	(1)	(1)	2	(0)	(0)	3	(1)	(2)	3	(0)	(0)	2	(0)	(0)
Other diseases*	34	6	12	13	15	62	13	8	31	12	25	83	13	0	0	11	0	27
Rheumatic infections, type VI, etc.	26	15	23	21	10	48	21	0	14	19	10	63	21	0	14	17	0	0
Acute streptococcic diseases, sinusitis	42	5	12	7	(0)	(5)	7	(0)	(4)	7	(2)	(6)	7	(0)	(1)	7	(0)	(0)

The figures in parentheses represent actual numbers.
* These diseases were: asthma, obesity, cardiovascular-renal disease and similar conditions.

TABLE 3.—*Percentage of Clinically Grouped Cases Yielding Serums Which Agglutinated with Selected Micro-Organisms (Based on Highest Agglutinin Titers for Each Case)*

Clinical Diagnosis	Str. Haemolyticus AB 13			Str. Haemolyticus W			Str. Viridans M			Str. Anhaemolyticus RB 5			Staph. Aureus P			Bact. Coli H		
	Total Cases	+320 or Over	All +	Total Cases	+320 or Over	All +	Total Cases	+320 or Over	All +	Total Cases	+320 or Over	All +	Total Cases	+320 or Over	All +	Total Cases	+320 or Over	All +
Arthritic Groups:																		
Type I	14	71	86	14	21	57	14	29	57	13	31	62	14	14	50	13	31	46
Type II	27	81	96	27	15	67	27	26	70	27	48	89	27	19	59	25	16	40
Type III	12	8	33	10	10	20	10	0	10	10	20	70	10	0	10	8	(1)	(1)
Type IV A	7	(2)	(4)	7	(2)	(4)	7	(1)	(2)	7	(2)	(6)	7	(1)	(3)	7	(1)	(3)
Type IV B	2	(0)	(1)	2	(1)	(1)	2	(0)	(0)	2	(0)	(1)	2	(0)	(0)	1	(0)	(0)
Type V	5	(0)	(2)	5	(0)	(2)	2	(0)	(0)	4	(2)	(4)	3	(0)	(1)	2	(0)	(0)
Control Groups:																		
Normal	39	0	3	6	(2)	(5)	6	(0)	(1)	6	(2)	(4)	6	(0)	(1)	6	(0)	(0)
Tuberculosis	18	0	5	3	(1)	(1)	2	(0)	(0)	3	(1)	(2)	3	(0)	(0)	2	(0)	(0)
Other diseases (general)	26	4	8	7	(2)	(4)	7	(1)	(3)	7	(3)	(7)	7	(0)	(0)	5	(0)	(1)
Rheumatic infections, type VI, etc.	16	25	31	11	18	64	11	0	18	10	20	70	11	0	27	7	(0)	(0)
Acute streptococcic diseases, sinusitis	20	10	25	7	(0)	(5)	7	(0)	(4)	7	(2)	(6)	7	(0)	(1)	7	(0)	(0)

The figures in parentheses represent actual numbers.

quent; when they occur in other clinical conditions, the titer is generally low and disappears rapidly.

In 28 cases of atrophic arthritis, in which the serums were tested against AB 13 at regular intervals, average agglutinin titers for each patient were computed. Ninety per cent of the cases showed an average titer of 1:320 or more, and in 100 per cent the reactions were positive in some degree. Forty random cases from all other groups were followed in a similar manner, and only 38 per cent showed a reaction; in 10 per cent the reaction was positive in high degree. The percentages were of course increased by the inclusion of group 4 A and the cases of rheumatic infection. Exclusive of these, the control figures are: positive reactions of any degree, 26 per cent of 30 cases; high positive reactions, 3 per cent.

The peak and average titers in 33 of 41 cases of atrophic arthritis were in general significantly higher for AB 13 than for any other test organism. The 8 remaining cases gave lower reactions with AB 13 than with other test organisms. Of the 8, 3 were definitely arrested cases; in 1 the patient had recovered; in 1 a high selectivity for Bact. coli H was consistently maintained, and 3 were active typical cases.

Because of a possible influence on agglutinin titers, all of the histories were searched for records of previous or concomitant streptococcic infections and of previous administrations of streptococcus vaccine. In groups 1 and 2 we were unable to find any subjects with a history of recent proved streptococcic infection, sore throats and colds being noticeably absent. There were only 12 patients of groups 1 and 2 to whom assuredly no vaccine had been given previous to the time of agglutination. Of these, 10 patients (83 per cent) proved to have high titer agglutinins for AB 13. Repeated agglutinin titers were determined at intervals on 46 patients with arthritis, 28 of whom had atrophic arthritis. In this group there was no regular correlation between agglutinin titer and clinical course. The agglutinin titer was seen to rise, fall or remain constant regardless of whether the clinical condition became worse or better or remained the same.

Our data, on analysis, showed no greater frequency of positive agglutinin reactions in the older patients than in the younger.

CUTANEOUS REACTIONS

To determine the number of organisms to be injected for cutaneous reactivity a group of 15 normal subjects was tested with phenol-saline preparations of the 6 different organisms previously described. In the case of AB 13 it was found that all normal subjects gave a small positive reaction to a dose of 20,000,000 organisms per one-tenth cubic centimeter, injected intracutaneously. When the dosage was reduced to

2,000,000 organisms, there were no positive reactions in the normal group. The skin test dose of 2,000,000 organisms was thus established and for uniformity was used with all autogenous and other stock organisms in testing patients. Readings were made at thirty minutes and at twenty-four and forty-eight hours. The induration and erythema of all of the reactions were measured and recorded in degrees from 1 plus to 4 plus. The standards for measurement were selected arbitrarily. Induration of from 0.4 to 0.7 cm. or erythema of from 0.6 to 1.5 cm. was considered 1 plus. Reactions with an induration of 1.9 cm. or erythema of 3.6 cm. or more were classed as 4 plus.

With the stock vaccines the positive reactions were few and scattered, without predominant reactions to any one organism in the arthritic group or in the controls. In the case of AB 13, 16 per cent of all patients with arthritis (i. e., 67) gave a positive reaction. In 31 cases of atrophic arthritis, 20 per cent of the patients gave positive reactions. This is higher than the percentage of positive reactions in the control group, but was not considered great enough to be of much significance. Surveying all of the cases, there was no apparent correlation between the skin test and the agglutinin titer.

In general, the group of patients with atrophic arthritis were strikingly anergic or nonreactive to the various organisms, both stock and autogenous. Only in rare instances was a cutaneous reaction to stock vaccine as strikingly positive as the reaction to the same number of autogenous organisms. In many instances the skin reacted to the autogenous organisms and not to the stock organisms when the dose was the same and the morphologic and cultural characteristics were similar. Positive reactions occurred more frequently with hemolytic gram-negative bacilli isolated from stools than with any other autogenous organisms.

TREATMENT WITH VACCINE

So much has been written about treatment with vaccine when all kinds of organisms, dosages and methods are used, that no attempt will be made to cover the literature. Except for a few well controlled experiments, the outstanding feature is the great diversity of reports. Many authors overlook the natural tendency in early cases to exacerbation and spontaneous remissions, which probably accounts for many of the reported cures and improvements. Sixty per cent of the 1,000 patients with arthritis who have been examined at the Desert Sanatorium recovered from the first attack.[18] The patients who were made worse by large doses of vaccine or nonspecific protein therapy were probably not reported. In our experience the best results have followed

18. Holbrook, W. P.: Evaluation of Therapy in Chronic Atrophic Arthritis, Ann. Int. Med. **7**:457 (Oct.) 1933.

desensitization of patients who have shown marked cutaneous sensitivity to an autogenous organism and occasionally to a stock organism. We have also observed that with subcutaneous and intramuscular injections the patient may do well for a time, but too often more sensitivity will develop. Clinically, there are increasing specific reactions to vaccine and increased cutaneous sensitivity to smaller doses.

On the basis of the aforementioned experiments and the experiments of Clawson and Weatherby [19] on animals, it was decided to confine treatment in this series to desensitizing doses by the intravenous route. Though we are aware that phenol-saline vaccine may not be the

TABLE 4.—*Serologic and Clinical Observations on a Few Representative Cases of Atrophic Arthritis*

Case	Duration, Years	Organisms Used in Treatment	Duration of Treatment, Months	Maximum Number of Organisms	Clinical Reaction to Vaccine	Skin Test		AB 13 Titer		Clinical Result
						Before Vaccine	After Vaccine	Before Vaccine	After Vaccine	
		Stock								
191	3	AB 13.....	4.5	50,000,000	0	+	0	1,280	1,280	Improved
186	6	AB 13.....	3.5	20,000,000	0	0	0	0	2,560	Improved
210	20	AB 13.....	1.0	30,000	+	++++	0	640	320	Worse
215	10	RB 5.....	2.0	1,000,000	0	0	0	640	1,280	Improved
176	26	B. coli H....	4.0	100,000,000	+	++	0	640	1,280	Improved
181	4	B. coli H....	5.0	100,000,000	+	+	0	640	640	No change
205	10	B. coli H....	2.0	5,000,000	+	++	0	640	640	Improved
207	13	B. coli H....	1.0	100,000	0	0	0	320	320	No change
		Autogenous								
202	2.5	Str. haemolyticus W	4.0	5,000,000	0	++++	0	0	2,560	No change
213	8	Hemolytic gram-negative bacilli	1.5	160,000	+	++++	0	1,280	160	Improved
183	14	Hemolytic gram-negative bacilli	5.0	10,000,000	+	++++	0	640	160	Improved
180	3	Hemolytic gram-negative bacilli	4.0	20,000,000	+	++++	++	640	1,280	Improved

ideal or correct preparation, we have used it because of our experience with it.

Comparable groups treated and untreated with vaccine were chosen for observation. All of the cases were chronic and of several years' duration. In addition each group was further subdivided to contain groups of patients with and without positive cutaneous reactions and groups of patients with and without positive agglutinin titers. All of the cases in which other modes of therapy might complicate the picture were ruled out.

In table 4 are listed observations on some of the typical cases of groups 1 and 2. The vaccine was given intravenously twice weekly,

19. Clawson, B. J., and Weatherby, M.: Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis with Summary of Results Obtained in Patients, Ann. Int. Med. **5**:1447 (June) 1932.

starting with approximately 100 organisms and gradually increasing to the maximum approximate dose listed over the period mentioned. An attempt to avoid apparently specific clinical reactions was made, though some reactions were noted with intravenous injections as low as from 30,000 to 50,000 organisms. Prior to and during the course of vaccine therapy repeated skin tests and agglutinin determinations were made on all of the patients. Cutaneous reactions and agglutinin titers before and after therapy were tabulated. The duration of therapy as listed does not represent the time during which the patients were under observation; as explained, all of the cases were chronic, and it is of importance that all of them were without significant change clinically for a period of at least a few months before the treatment with vaccine was started. In our experience the patients who respond well to vaccine show evidence of it within a month or two.

RESULTS OF TREATMENT WITH VACCINE

So far in this work we have not a sufficiently large group of well controlled cases from which to draw conclusions of much clinical significance. Several observations were made, however, that are worth noting. Sensitivity to a particular organism was reduced in every case following the intravenous administration of the same organism; this desensitization did not occur in a few instances in which heterologous organisms were given intravenously or in which homologous organisms were given subcutaneously. There was no regularity in changes of agglutinin titer during or after treatment with vaccine; the titer increased, decreased or remained constant without apparent relation to the treatment with vaccine or the clinical course. The clinical course of the patient and the result listed in the table may or may not be due to treatment with vaccine, for here again comparable groups of patients not receiving vaccine did quite as well. Skepticism is invited because of the well known psychologic effects of a new treatment on patients with chronic conditions. There is no case in the table or in the balance of unlisted patients in which improvement could not have been caused by some factor or factors other than vaccine. We believe, however, although we cannot prove, that in some of the patients who showed marked cutaneous sensitivity, significant improvement followed desensitization. The improvement that seemed most probably due to treatment with vaccine was obtained with autogenous organisms only.

COMMENT

The foregoing observations on a representative group of arthritic patients indicate that Str. haemolyticus AB 13 has a closer serologic relation to atrophic arthritis than any other organism studied. This is in agreement with the reports of Cecil and his co-workers and the

experiments of Dawson and Boots. We feel that the relatively high percentage of positive reactions with RB 5 was insignificant, as it showed no selectivity for any clinical group. Other organisms were of possible serologic interest only in isolated cases.

If there is a definite bacterial agent responsible for arthritis, three possibilities occur to us in explanation of the serologic behavior of AB 13 in the disease: 1. It is the cause of atrophic arthritis; recognizing that highly selective serologic reactions are not necessarily indicative of etiologic relations, we feel that definite deductions on this point would be premature. 2. In specific protein content, AB 13 is related to this agent. 3. AB 13 may be a secondary invader, its existence made possible in the human body by the previous production of highly specific conditions favorable to its growth. Such conditions once established, antigen could readily be released into the system, producing apparently specific agglutinins. In this connection it must be remembered that this streptococcus is not a common inhabitant of the human body, and that it cannot readily be cultured from any of the common sources.

It seems probable that the occurrence of AB 13 agglutinins in atrophic arthritis is not solely explainable on the basis of so-called normal antibodies. The AB 13 titer is in a large percentage of cases of atrophic arthritis within a titer range generally considered indicative of serologic specificity (320 or more), while in other clinical groups tested the serum titers for this organism are uniformly low or negative. The AB 13 titers of serums from patients with atrophic arthritis are higher than titers for any other organisms employed in this study, although the remaining organisms, particularly Staph. aureus and Bact. coli, occur among the common flora of the human body. Mackie and Finkelstein [20] and Gibson,[21] in their discussions of the natural phenomena of immunity, agreed that normal antibodies, though occurring frequently in the blood of various mammals, are most readily demonstrable for bacteria of the intestinal groups. We found few agglutinins against Bact. coli and Staph. aureus in the atrophic group. Gibson reported no natural agglutinin titers higher than 320 except in a few cases with Bacillus pyocyaneus and Bacterium dysenteriae; his series comprised a large and representative group of bacterial species. He further stated that the serums of young animals are deficient in natural agglutinins. We were unable to demonstrate that the age group plays a part in the occurrence of AB 13 agglutinins in the patients with atrophic arthritis or in the remainder of the clinical groups studied; this is contrary to a recent report by Dawson, Olmstead and Boots.

The absence of correlation between agglutinin titer and cutaneous sensitivity in arthritis is not surprising when one considers that such a

20. Mackie, T. J., and Finkelstein, M. H.: J. Hyg. **30**:1, 1930.
21. Gibson, H. J.: J. Hyg. **30**:337, 1930.

relation is not reported in other chronic diseases. We have frequently noted that cutaneous sensitivity diminished with the intravenous administration of vaccine, but that the agglutinin titer showed no corresponding variations.

There was no correlation between agglutinin titer and cutaneous reaction in a group of over 100 patients, all of whom were tested by the two methods simultaneously at least once. The same finding applies to a group of 31 atrophic patients tested in a similar fashion at weekly intervals for several months. Likewise, Keefer, Myers and Oppel,[22] in using the nucleoprotein of Str. scarlatinae, found no correlation between skin tests and agglutinations.

It has been reported that a fall in the agglutinin titer often accompanies clinical improvement. We are not able to substantiate this observation, as we have noted a stationary and a rising titer with definite clinical improvement. As has been mentioned, in one group of patients there was a marked fluctuation in the agglutinin titer, although there was no apparent change in the clinical course. This was even apparent in a group of 6 patients tested at two day intervals for a period of two weeks.

Positive cutaneous reactions were more frequent and more marked in the group of patients with atrophic arthritis than in the control group but, as was explained earlier, the difference did not seem great enough to be worthy of consideration. Keefer, Myers and Oppel [22] also reported comparisons of cutaneous with agglutination reactions in rheumatoid arthritis and rheumatic fever. Their use of the nucleoprotein of Str. scarlatinae may account for their greater percentage of positive reactions in these diseases as well as in acute respiratory diseases associated with Str. haemolyticus. We have noted a few large cutaneous reactions occurring within thirty minutes on several patients with atrophic arthritis; thus we agree with Keefer, Myers and Oppel that there may be an allergic factor.

In the group of patients given vaccine intravenously only a few showed a definite and constant rise in agglutinin titer. This rise was not necessarily associated with large doses, for in some cases in which the doses were as low as approximately 5,000,000 organisms it was marked and persistent, whereas in other cases in which the dosage reached 100,000,000 organisms and was continued for a long period no rise was noted. It may be of importance to mention again that all of these observations were made on patients treated intravenously; vaccine given subcutaneously or intramuscularly may have a different effect on the agglutinin titer.

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22. Keefer, C. S.; Myers, W. K., and Oppel, T. W.: J. Clin. Investigation **12**:279, 1933.

Ordinarily a laboratory procedure is unnecessary in establishing a diagnosis of arthritis. Occasionally, in doubtful cases, when the facilities of a laboratory are available, the AB 13 agglutinin titer may be an additional aid. After the diagnosis has been well established, the agglutinin titer has doubtful prognostic value because of the frequent extreme fluctuations of titer apparently unrelated to the clinical course. If this test is used to corroborate the diagnosis of early clinical stages, it should be applied under carefully controlled conditions in the laboratory and under the supervision of an experienced serologist. Accurate reading of the agglutination of streptococci presupposes a definite familiarity with the positive serologic picture produced by the particular organism involved. For this reason, the technic of the test does not lend itself to the conditions of an occasional isolated procedure in the laboratory.

CONCLUSIONS

1. Cecil's hemolytic streptococcus AB 13 shows a greater serologic selectivity for atrophic arthritis than for any other disease group studied, as evidenced by the percentage of positive reactions in high agglutinin titer.

2. The percentage of serums of patents with atrophic arthritis which contain agglutinins in high titer for AB 13 cannot be accounted for on the basis of (*a*) previous artificial immunization or (*b*) previous or concomitant streptococcic infections.

3. No other organism employed in this work was as selective as AB 13 for serums from patients with atrophic arthritis either in the height of the serum titer or in the frequency of positive agglutinin reactions.

4. No correlation was found between agglutinin titers and cutaneous reactions to vaccine of homologous organisms in the patients with atrophic arthritis.

5. Often within a short time a striking unexplained variation of agglutinin titers, not accounted for by clinical developments, occurs in patients untreated by vaccine.

6. In this study there was no regularity in the changes in the agglutinin titer as a result of vaccine therapy.

7. There is no apparent relationship between the variation in agglutinin titer and the clinical course.

8. A few patients seemed to be benefited by desensitization with vaccine. The improvement in other patients who received vaccine therapy may have been due to other factors impossible to control.

9. The AB 13 agglutinin titer has a definite but limited use as a diagnostic aid in arthritis.

ACTION OF DIURETIC DRUGS

I. ACTION OF DIURETICS IN NORMAL PERSONS

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The various diuretics are of great clinical value in a wide variety of pathologic states, but the exact conditions which are most favorable for their action and the nature and mechanism of their action remain to a large extent obscure. One of the reasons for the unsatisfactory state of our knowledge is that the diseased states affected by the diuretic drugs vary from patient to patient, and, indeed, in the same patient. Consequently it is difficult to be certain as to what extent the changes following the administration of diuretics are due to those drugs and to what extent they result from spontaneous changes in the pathologic physiology of the conditions under investigation. Furthermore, complete studies of water and salt metabolism are so intricate that most of the investigations on the effect of diuretics are fragmentary and inconclusive.

It appeared desirable, therefore, to undertake a study of the various diuretics under conditions which are constant and readily reproducible. Previous work on the effect of extract of the posterior lobe of the pituitary gland on water and salt metabolism [1] has shown that such conditions can best be obtained with normal persons. For these reasons, the present studies, which form the basis of further observations in pathologic conditions with edema, were undertaken on normal subjects.

From the clinical point of view we have been interested in the character, magnitude and duration of the effect of the diuretic drugs, as

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From the Medical Research Laboratories and the medical service of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School.

1. Gargle, S. L.; Gilligan, D. R., and Blumgart, H. L.: The Antidiuretic Effect of the Oxytocic and Pressor Principles of the Extract of the Posterior Lobe of the Pituitary, New England J. Med. **198**:169, 1928.

well as in the existence of any untoward reactions. From the physiologic point of view information has been sought in regard to the mechanism of action of these drugs. Four different diuretics have been administered, namely, salyrgan and merbaphen of the mercurial group, and metaphyllin (theophylline ethylenediamine) and theobromine sodium salicylate of the xanthine group.

PROCEDURE

The physical environment under which the action of the diuretics was studied was kept as constant as possible in order that the changes produced by the diuretics would not be obscured by relatively large fluctuations such as exist in the usual clinical environment. The subjects were placed in a metabolism room and confined to bed except for short periods each day. The room temperature was observed every four hours and did not exceed 78 F. at any time.

The three normal adult men chosen as suitable for the study showed no evidence of renal or cardiac abnormalities. The subjects were well nourished, had normal basal metabolic rates and were intelligent and cooperative. E. W. previously had had acute nephritis, but he showed no evidence of renal damage at the time of the study.

Since the purpose of a diuretic is to remove abnormal deposits of body fluids without disturbing the normal composition of the remaining fluid matrix, it is essential that the drug should remove not only water but also the substances dissolved in the water. To learn to what extent the various common diuretics fulfil this essential requirement, we have studied all the electrolyte constituents of the urine which are present in important amounts in body fluids.

The observations reported in the literature on the effect of diuretics on water and mineral metabolism in man have generally been made on twenty-four hour specimens of urine. Our previous studies [1] of the effect of extract of the posterior lobe of the pituitary have demonstrated the necessity of collecting the urine at frequent stated intervals during the twenty-four hour period in order to evaluate the effect of this drug accurately. Marked changes in water and salt metabolism caused by a single dose of pituitary extract were followed in a few hours by equally marked changes in the opposite direction, so that no effects were obvious in the amount of urine collected in twenty-four hours. It was considered of the utmost importance, therefore, in studying the effect of the diuretics on the water and salt metabolism, to divide the observations into short periods of time, as they are presented in table 1.

The study of specimens of urine collected at repeated intervals during the day permits a more accurate estimation of the duration of the diuretic effect, and also enables one to learn whether the general nature of the diuresis is the same in the initial as in the later periods.

A carefully weighed neutral diet (table 2), adequate in all respects, was given at specified times each day, and on no occasion was food returned uneaten. The subjects received the same articles of food every day, the three meals differing from each other but being exactly the same from day to day. This diet was so designed as to permit its use in other studies on patients with nephritis and cardiovascular disease. The diet was planned to contain small amounts of sodium and chloride, and the necessary requirements were met by adding salt in the form of chemically pure sodium chloride, thereby reducing variations in the intake of salt to a minimum.

TABLE 1.—*Daily Schedule*

7:00 a. m.	Void
7:30 a. m.	Breakfast
9:30 a. m.	Void
9:30 a. m.	333 cc. water
12:00 noon	Void
12:00 noon	Dinner
2:00 p. m.	Void
2:30 p. m.	333 cc. water
4:30 p. m.	Void
4:30 p. m.	Supper
6:30 p. m.	Void
7:30 p. m.	334 cc. water
9:00 p. m.	Void

TABLE 2.—*Total Daily Dietary Intake Used Throughout the Studies*

Subject	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Chloride		Sodium		Potassium		Calcium, Calculated, M.Eq.	Magnesium, Calculated, M.Eq.	Phosphorus, Calculated, M.Eq.	Sulphur, Calculated, M.Eq.	Water	
					Calculated, M.Eq.	Analyzed, M.Eq.	Calculated, M.Eq.	Analyzed, M.Eq.	Calculated, M.Eq.	Analyzed, M.Eq.					Calculated, Gm.	Analyzed, Gm.
S. D.	66	105	254	2,230	69	82	75	75	69	57	24	17	54	56	1,521	1,466
S. A.	66	80	224	1,880	69	82	75	75	69	57	24	17	54	56	1,521	1,466
E. W.	46	69	141	1,320	62	68	101	100	30	28	19	9	37	40	1,080	1,005

Exact duplicates of the diet were analyzed chemically on several occasions to make certain of the actual total intake of the most important inorganic constituents. The values used for the calculation of this diet were obtained in part from analyses made by Aub,[2] and in part from Sherman's tables.[3] The calculated water contents were obtained from circulars from the United States Department of Agriculture.[4] The analytic values for the potassium and chloride contents

2. Aub, J. C.: Personal communication to the authors.

3. Sherman, H. C.: Chemistry of Food and Nutrition, New York, The Macmillan Company, 1928.

4. United States Department of Agriculture Circulars nos. 50 (Dec. 1928), 146 (Jan. 1931) and 389 (July 1926).

of the diets differed somewhat from the calculated values (table 2). The constancy of the diet was demonstrated by the close agreement of the results of analyses made during different periods of the study. In addition to the water supplied in the diet, 1 liter of water divided into three equal portions was given to each subject at specified times during the day (table 1).

The daily schedule given in table 1 was adhered to strictly. No medication, except the diuretics studied, was given. No quantitative studies were made until the subjects had been on the metabolic regimen for a week or more. Preliminary measurements were then made until the subjects were in satisfactory equilibrium with the conditions of the study. Measurements of the volume and of the various constituents of each specimen of urine were then made for several days before a diuretic was administered, to learn the extent of the spontaneous variations under the fixed conditions of the experiment.

METHODS

The specimens of urine were collected directly in bottles containing toluene as a preservative. The ammonia content and titratable acidity were determined when specimens were fresh. The chloride content was also usually determined within twenty-four hours after voiding, and a small amount of concentrated hydrochloric acid was then added to each specimen as an additional preservative, and to prevent the precipitation of alkaline phosphates.

Stools were demarcated by the oral administration of 1 Gm. of ashless lampblack charcoal at the beginning and at the end of each period of observation. They were weighed shortly after passage to prevent a loss of water by evaporation.

Body weights were determined daily, and at additional times when desired, by means of a beam balance which gave results accurate to approximately 1 Gm.

The chemical methods used for the analyses of urine were as follows: ammonia, Van Slyke and Cullen;[5] chloride, Folin;[6] inorganic phosphorus, Fiske and Subbarow;[7] inorganic sulphate, Fiske;[8] potassium, Fiske and Litarczek;[9] sodium, Butler and Tuthill;[10] titratable acidity minus carbon dioxide by adding 5 cc. of one-tenth normal hydrochloric acid to 25 cc. of urine, blowing off carbon dioxide and titrating to p_H 7.38 with one-tenth normal sodium hydroxide, using phenol-

5. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use in the Determination of Urea, J. Biol. Chem. **19**:211, 1914; The Determination of Urea by the Urease Method, ibid. **24**:117, 1916.

6. Folin, O.: Simplified Chlorid Determination in Laboratory Manual of Biological Chemistry, ed. 4, New York, D. Appleton and Company, 1926, p. 167.

7. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

8. Fiske, C. H.: The Determination of Inorganic Sulphate, Total Sulphate and Total Sulphur in Urine by the Benzidine Method, J. Biol. Chem. **47**:59, 1921.

9. Fiske, C. H., and Litarczek, G.: Unpublished data.

10. Butler, A. M., and Tuthill, Elizabeth: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, J. Biol. Chem. **93**:171, 1931.

sulphonphthalein as an indicator and a standard phosphate buffer for color comparison, a modification of the method of Henderson and Palmer;[11] calcium, Fiske and Logan;[12] total nitrogen, Folin;[13] urea clearance, Möller, McIntosh and Van Slyke[14] and McIntosh, Möller and Van Slyke,[15] and creatinine, Folin.[16] The same methods, with slight modifications when necessary, were used for analyses of stools. The stools were ashed by the nitric acid wet ash method. The results of the analyses of the various constituents in the individual specimens of urine were checked by comparison with the results found for a representative twenty-four hour amount obtained by combining 10 per cent of the volume of each individual specimen. The analyses of stools were made in duplicate on the ashed extracts.

The serum constituents were determined by the following procedures: chloride, Wilson and Ball;[17] sodium, Rourke;[18] specific gravity (bottles containing 5 cc. were used), Moore and Van Slyke;[19] creatinine, Folin,[20] and protein, Dyer.[21] All the analyses of serum were made in duplicate. The accuracy of the chemical methods employed in all the studies was confirmed by analyzing known solutions at frequent intervals during the course of the investigation.

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11. Henderson, L. J., and Palmer, W. W.: On the Several Factors of Acid Excretion, J. Biol. Chem. **17**:305, 1914.

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13. Folin, O.: Total Nitrogen Determination in Urine by Direct Nesslerization, in Laboratory Manual of Biological Chemistry, New York, D. Appleton and Company, 1926.

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The rates of glomerular filtration were measured by the method of Rehberg,[22] slightly modified, in that no creatinine was fed, and the creatinine contents of the serum and urine were determined by the methods of Folin.[23]

Owing to the many extraneous factors which affect water and salt metabolism, even under the rigidly controlled conditions of this study, the urinary outputs of water and inorganic salts showed variations for single periods, which were, at times, considerable. For this reason, the average urinary findings for the individual periods of the several control days, before the diuretic was administered, were used as the basis of comparison. In this way a base line was established, according to which the diuretic effect of the drug administered could be gaged more accurately.

In accord with these considerations the net quantitative effect of the diuretics was measured *by the increases above or the decreases below the average excretion* during corresponding periods on the control days immediately preceding the medication. In presenting the results, the amounts above or the amounts below the corresponding average figures of the original preliminary control periods have been charted (figs. 1 to 9), rather than the total amounts excreted.

The data have also been analyzed to gain information as to the source of the increased output of water and inorganic salts following the administration of the diuretics. The measurements of the urine include the constituents which occur in important amounts in body fluids, namely chloride, sodium, potassium and calcium. In addition to these constituents, the amounts of other substances in the urine, the excretion of which is important in maintaining the constancy of the acid-base equilibrium of the body, have been determined. These include inorganic phosphate, inorganic sulphate, ammonia, titratable acid (minus carbon dioxide) and total nitrogen.

RESULTS

In the following presentation of results, the data for the water, sodium, chloride, potassium and calcium in the urine will be discussed for each experiment. The findings in regard to the urinary excretion of inorganic phosphate, inorganic sulphate and ammonia and the titratable acidity and specific gravity of the urine will be discussed together later.

Effect of Merbaphen on S. D.—The administration of 2 cc. of merbaphen intravenously caused an increase in the volume of urine (table 3) during the first seven hours after the injection of the drug, accompanied by a conspicuously increased excretion of sodium, chloride,

22. Rehberg, P. B.: Studies on Kidney Function: I. The Rate of Filtration and Reabsorption in the Human Kidney, Biochem. J. **20**:447, 1926.

23. Folin (footnotes 16 and 20).

potassium and calcium (fig. 1). There was a relatively constant relationship between the increases in the excretion of chloride, sodium and calcium during the different periods of diuresis (fig. 1). This indicates that the diuresis was not primarily a diuresis of chloride or of any other single constituent. The increase in the excretion of potassium appeared somewhat later and persisted after the period of diuresis of water, sodium, chloride and calcium. Immediately following the increased

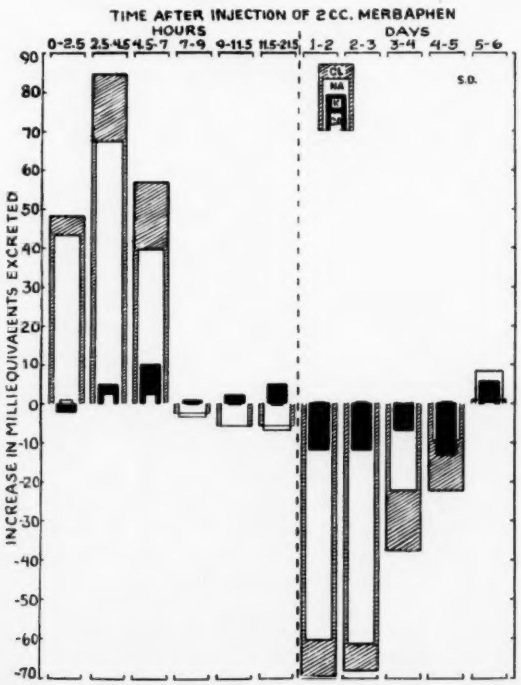

Fig. 1.—Net effect of the intravenous administration of 2 cc. of merbaphen on the urinary excretion and subsequent retention of chloride, sodium, potassium and calcium in S. D. In this and in all the following figures the amounts above or below the average values for the corresponding control periods have been charted. The figures represent, therefore, the net effect of the action of the drug on those constituents of the body. The effect of the diuretics on the excretion of inorganic phosphate, inorganic sulphate and ammonia and on the titratable acidity was much less significant and has not been charted.

excretion there was a compensatory diminution in the output of these substances lasting for four days. This period of retention restored to the body the substances which had been lost during the period of diuresis. The restraining factor which prevented a more rapid

restoration of the lost body fluid was evidently the restricted intake of sodium chloride. This fact is demonstrated by the failure to retain available water in the absence of corresponding amounts of salt, for the volume of urine was relatively great in view of the nearly complete absence of sodium and chloride in the urine during the first two days following the diuresis (table 3). Furthermore, as evident from the divided specimens of urine on the first day following the diuresis (table 3), there was almost complete retention of available sodium and chloride during the periods immediately following meals, as well as in the intervals.

The studies of Gamble, Ross and Tisdall [24] have added considerable significance to measurements of the excretion of sodium and potassium. Potassium is the predominant base in cells,[25] while sodium predominates in blood plasma and other extracellular fluids. In edema fluid, which may be taken as an example of extracellular fluid, sodium and potassium are present in concentrations of approximately 145 and 4 milliequivalents per liter of water, respectively, according to results obtained by workers in our laboratory [26] and by Greene and his co-workers.[27] According to Peters,[28] the base of cells is probably almost entirely potassium. The concentration of total base throughout the body fluids is approximately the same. It may be assumed, therefore, that the potassium of cell water is approximately 160 milliequivalents per liter.

The increase in the amount of sodium excreted by the subject S. D. during the seven hours of diuresis following the administration of 2 cc. of merbaphen was 3.5 Gm., or approximately 150 milliequivalents; the increase in the amount of potassium excreted simultaneously was 0.5 Gm., or approximately 13 milliequivalents. Applying these data to the aforementioned considerations, it is apparent that the amount of sodium excreted during the diuresis, namely 150 milliequivalents, is equivalent to the sodium content of 1,030 cc. ($\frac{150}{145} \times 1{,}000$) of interstitial fluid. The potassium content of this amount of interstitial fluid would be approximately 4 milliequivalents. The remaining 9 milliequivalents of potassium excreted during the diuresis was presumably

24. Gamble, J. L.; Ross, G. S., and Tisdall, F. F.: Metabolism of Fixed Base During Fasting, J. Biol. Chem. **57**:633, 1923.

25. Katz, J.: Die mineralischen Bestandtheile des Muskelfleisches, Arch. f. d. ges. Physiol. **63**:1, 1896.

26. Gilligan, D. Rourke; Volk, M. C., and Blumgart, H. L.: Observations on the Chemical and Physical Relation Between Blood Serum and Body Fluids: I. The Nature of Edema Fluids and Evidence Regarding the Mechanism of Edema Formation, J. Clin. Investigation **13**:365, 1934.

27. Greene, C. H.; Bollman, J. L.; Keith, N. M., and Wakefield, E. G.: The Distribution of Electrolytes Between Serum and Transudates, J. Biol. Chem. **91**: 203, 1931.

28. Peters, J. P.: Personal communication to the authors.

TABLE 3.—*Effect of Diuretics on the Urinary Excretion of S. D.*

Date, 1931	Medication	Time of Voiding	Volume, Cc.	Specific Gravity	Chloride, M.Eq.	Sodium, M.Eq.	Potassium, M.Eq.	Calcium, M.Eq.	Ammonia Nitrogen, M.Eq.	Titratable Acidity Minus Carbon Dioxide, M.Eq.	Inorganic Phosphate Phosphorus,* M.Eq.	Inorganic Sulphate Sulphur, M.Eq.	Total Nitrogen, Gm.
5/19	.....	9:30 a. m.	86	1.025	12.2	10.3	7.2	...	2.7	+ 2.6	4.6		
		12:00 noon	90	1.020	15.2	7.2	11.5	...	2.6	+ 1.9	3.3		
		2:00 p. m.	150	1.012	9.7	9.3	5.3	...	2.3	+ 4.2	5.9		
		4:30 p. m.	314	1.007	11.3	12.0	4.1	...	3.7	+ 3.4	7.1		
		6:30 p. m.	204	1.005	7.8	6.0	2.1	...	3.4	+ 3.2	3.8		
		9:00 p. m.	341	1.004	7.8	9.8	2.1	...	3.6	+ 2.3	4.5		
		7:00 a. m.	156	1.024	6.6	8.4	9.6	...	10.6	+ 1.3	11.8		
		Total.....	1,341	1.011	70.6	63.0	41.9	5.2	28.9	+18.8	41.0	....	9.4
5/20	.....	9:30 a. m.	69	1.025	9.3	7.5	6.0	...	3.3	+ 4.9	3.6	3.9	
		12:00 noon	63	1.027	10.3	4.1	9.5	...	3.1	+ 2.4	2.6	3.3	
		2:00 p. m.	99	1.026	18.6	15.2	8.7	...	2.5	+ 3.8	7.0	4.0	
		4:30 p. m.	61	1.028	8.5	8.8	7.1	...	1.5	+ 1.2	2.9	3.4	
		6:30 p. m.	101	1.017	8.2	8.1	4.6	...	3.5	+ 3.2	4.6	3.7	
		9:00 p. m.	397	1.005	9.2	13.4	2.6	...	3.6	+ 1.9	4.2	3.5	
		7:00 a. m.	151	1.026	6.8	9.1	9.3	...	11.2	+ 8.7	10.3	10.7	
		Total.....	941	1.018	70.9	66.2	47.8	5.8	28.7	+26.2	35.2	32.5	8.7
5/21	.....	9:30 a. m.	72	1.023	10.7	9.1	5.6	1.2	2.8	+ 2.4	3.5	3.7	
		12:00 noon	140	1.017	27.2	20.0	13.8	1.0	2.9	— 3.2	3.1	4.2	
		2:00 p. m.	145	1.015	14.6	16.4	6.4	0.7	2.0	+ 6.4	6.4	2.7	
		4:30 p. m.	303	1.005	8.6	9.5	4.8	0.5	3.0	+ 1.0	3.6	2.4	
		6:30 p. m.	166	1.007	8.9	8.5	3.2	0.6	4.1	+ 2.0	3.5	3.0	
		9:00 p. m.	342	1.003	5.1	8.2	3.1	0.4	4.0	+ 1.5	3.3	4.0	
		7:00 a. m.	167	1.007	5.0	5.5	10.0	0.6	12.0	+ 8.4	10.3	10.9	
		Total.....	1,333	1.012	80.1	77.2	46.9	5.0	30.8	+18.5	33.7	30.9	7.8
5/22	Merbaphen, 2 cc. intravenously at 9:30 a. m.	9:30 a. m.†	76	1.024	10.7	9.0	6.3	1.2	2.9	.....	3.9	3.8	
		12:00 noon	355	1.019	65.7	53.9	9.5	1.9	5.9	— 1.5	1.9	2.5	
		2:00 p. m.	482	1.007	99.1	80.9	11.5	3.3	4.3	+ 2.8	3.7	2.2	
		4:30 p. m.	525	1.006	66.2	49.5	15.3	3.0	5.0	+ 3.0	4.5	3.2	
		6:30 p. m.	81	1.015	5.8	4.1	4.1	0.5	3.4	+ 1.7	2.5	3.2	
		9:00 p. m.	321	1.005	1.5	....	....	...	4.4	+ 2.7	4.6	2.1	
		7:00 a. m.	154	1.024	0.7	0.8	14.5	0.3	13.0	+10.0	14.8	11.8	
		Total.....	1,994	1.008	249.7	....	....	...	38.9	.....	35.9	28.8	7.6
5/23	.....	9:30 a. m.	58	1.029	0.7	0.8	4.6	1.0	3.9	+ 3.5	4.9	4.4	
		12:00 noon	210	1.008	0.8	1.0	3.6	1.1	4.1	+ 1.3	3.0	2.9	
		2:00 p. m.	82	1.022	0.4	0.9	8.9	0.6	3.3	+ 3.3	6.4	3.0	
		4:30 p. m.	236	1.009	0.7	1.2	5.1	0.6	4.7	+ 3.0	6.2	3.4	
		6:30 p. m.	162	1.008	0.4	0.7	2.8	0.5	3.7	+ 2.1	4.2	2.7	
		9:00 p. m.	360	1.005	0.7	2.8	3.9	0.6	5.6	+ 3.7	6.3	4.4	
		7:00 a. m.	150	1.023	0.6	0.9	9.7	0.9	13.4	+ 8.2	11.8	10.4	
		Total.....	1,258	1.010	4.3	8.3	33.6	5.3	38.7	+25.0	42.8	31.2	8.5
5/24	.....	Total.....	980	1.010	5.7	7.5	33.5	5.5	33.0	+20.2	37.7	....	8.0
5/25	.....	Total.....	1,026	1.011	35.9	46.4	38.7	4.9	28.3	+14.0	36.3	....	8.3
5/26	.....	Total.....	1,252	1.012	51.0	59.2	32.4	5.7	28.0	+12.6	37.5	....	8.5
5/27	.....	Total.....	1,060	1.014	74.9	77.1	51.2	5.8	32.6	+22.8	40.9	....	9.9

6/ 6	.....	9:30 a. m.	93	1.020	14.9	11.6	8.2	...	....	.....	4.5		
		12:00 noon	207	1.007	15.9	9.4	11.4	...	....	.....	1.7		
		2:00 p. m.	57	1.025	7.0	7.8	3.8	...	....	.....	4.5		
		4:30 p. m.	275	1.006	10.3	5.2	8.8	...	....	.....	5.3		
		6:30 p. m.	80	1.017	5.9	6.8	2.6	...	....	.....	5.2		
		9:00 p. m.	314	1.003	9.6	14.9	3.6	...	....	.....	5.5		
		7:00 a. m.	146	1.022	6.2	8.0	9.0	...	....	.....	12.2		
		Total.....	1,172	1.012	69.8	63.7	47.4	5.5	28.9	+24.6	38.9	....	8.5
6/ 7	.....	9:30 a. m.	53	1.030	6.1	3.4	5.2	...	....	.....	4.4	3.7	
		12:00 noon	105	1.015	14.7	10.0	10.2	...	....	.....	2.7	2.7	
		2:00 p. m.	363	1.005	17.2	16.1	10.7	...	....	.....	7.1	2.4	
		4:30 p. m.	152	1.007	4.4	2.9	5.0	...	....	.....	4.2	2.3	
		6:30 p. m.	211	1.004	6.3	8.4	4.1	...	....	.....	5.0	2.8	
		9:00 p. m.	454	1.001	9.1	12.2	4.2	...	....	.....	3.9	3.1	
		7:00 a. m.	219	1.013	14.0	15.7	10.4	...	....	.....	11.5	12.6	
		Total.....	1,557	1.010	71.8	68.7	49.8	...	30.7	+26.7	38.8	29.6	8.9
6/ 8	.....	9:30 a. m.	63	1.027	7.1	5.9	6.7	1.0	2.7	.....	4.9	3.5	
		12:00 noon	146	1.016	15.0	6.9	14.8	0.6	2.9	.....	4.9	3.1	
		2:00 p. m.	185	1.012	4.4	8.4	6.2	0.8	3.4	.....	10.6	3.9	
		4:30 p. m.	130	1.011	3.5	3.5	3.8	0.6	3.1	.....	3.6	1.9	
		6:30 p. m.	373	1.003	4.7	5.6	2.4	0.7	3.4	.....	3.1	1.9	
		9:00 p. m.	610	1.004	12.2	23.2	6.8	0.7	2.4	.....	5.5	4.0	
		7:00 a. m.	206	1.019	13.8	23.2	9.2	1.0	9.5	.....	11.9	9.7	
		Total.....	1,713	1.011	60.7	76.7	49.9	5.3	27.4	+27.4	44.5	28.0	8.6
6/ 9	Metaphyllin, 2 cc. Intravenously at 9:30 a. m.	9:30 a. m.	132	1.021	19.9	15.9	8.5	1.1	2.9	.....	5.3	4.0	
		12:00 noon	562	1.011	61.1	53.3	17.8	2.7	2.5	.....	4.1	3.5	
		2:00 p. m.	400	1.014	43.6	47.7	9.4	1.9	2.0	.....	10.1	3.4	
		4:30 p. m.	526	1.006	18.5	21.0	9.4	1.0	1.6	.....	4.8	2.2	
		6:30 p. m.	114	1.015	9.0	10.0	3.0	0.4	2.8	.....	5.3	2.9	
		9:00 p. m.	435	1.006	12.2	18.0	4.1	0.8	3.1	.....	8.4	5.0	
		7:00 a. m.	140	1.026	3.4	6.6	13.0	0.4	9.5	.....	12.8	10.6	
		Total.....	2,309	1.010	167.7	172.5	65.2	8.3	24.4	.....	50.8	30.6	9.6
6/10	.....	Total.....	753	1.010	13.2	15.4	29.5	3.8	30.2	.....	33.1	34.7	9.4
6/11	.....	Total.....	1,018	1.014	28.0	17.6	34.3	5.0	32.6	.....	40.9	....	9.5
6/12	.....	Total.....	1,275	1.012	44.1	35.3	43.7	5.8	36.5	.....	44.9	....	9.2
6/13	.....	Total.....	2,104	1.010	111.5	100.6	57.0	...	31.9	+11.4	44.2	....	9.7

* The valence was assumed to be 1.8.
† Some of the urine was lost for this period, and the figures given are calculated from results on preceding days.

TABLE 3.—*Effect of Diuretics on the Urinary Excretion of S. D.—Concluded*

Date, 1931	Medication	Time of Voiding	Volume, Cc.	Specific Gravity	Chloride, M.Eq.	Sodium, M.Eq.	Potassium, M.Eq.	Calcium, M.Eq.	Ammonia Nitrogen, M.Eq.	Titratable Acidity Minus Carbon Dioxide, M.Eq.	Inorganic Phosphate Phosphorus,* M.Eq.	Inorganic Sulphate Sulphur, M.Eq.	Total Nitrogen, Gm.
6/28	.....	9:30 a. m.	86	1.019	6.8	5.5	....	...	....	.....	4.7		
		12:00 noon	241	1.009	20.1	12.4	....	...	....	.....	3.3		
		2:00 p. m.	353	1.008	19.1	20.8	....	...	....	.....	7.5		
		4:30 p. m.	249	1.006	8.3	10.8	....	...	....	.....	3.9		
		6:30 p. m.	340	1.002	4.8	5.8	....	...	....	.....	3.7		
		9:00 p. m.	161	1.011	7.3	9.4	....	...	....	.....	5.3		
		7:00 a. m.	139	1.020	3.1	2.4	....	...	....	.....	11.4		
		Total.....	1,569	1.007	69.5	67.1	45.0	...	26.2	+11.2	39.8	....	7.9
6/29	... .	9:30 a. m.	66	1.023	8.7	6.8	....	...	....	.....	3.4		
		12:00 noon	127	1.017	17.2	9.2	....	...	....	.....	3.1		
		2:00 p. m.	478	1.006	17.8	16.1	....	...	....	.....	6.2		
		4:30 p. m.	455	1.007	22.6	25.6	....	...	....	.....	4.9		
		6:30 p. m.	208	1.007	9.8	11.1	....	...	....	.....	3.6		
		9:00 p. m.	118	1.011	8.1	10.2	....	...	....	.....	3.7		
		7:00 a. m.	147	1.021	2.8	1.4	....	...	....	.....	12.2		
		Total.....	1,599	1.008	87.0	80.4	42.8	...	28.7	+14.4	37.1	....	8.1
6/30	....	9:30 a. m.	51	1.025	3.9	3.2	....	...	3.4	.....	4.3		
		12:00 noon	312	1.007	16.7	8.2	....	...	4.0	.....	4.1		
		2:00 p. m.	245	1.008	10.3	11.0	....	...	2.8	.....	6.3		
		4:30 p. m.	395	1.005	14.2	12.9	....	...	2.9	.....	4.4		
		6:30 p. m.	435	1.004	5.7	7.3	....	...	3.3	.....	4.2		
		9:00 p. m.	157	1.011	7.5	11.4	....	...	4.3	.....	4.1		
		7:00 a. m.	159	1.024	3.1	2.4	....	...	13.2	.....	16.1		
		Total.....	1,754	1.011	61.4	56.4	52.0	...	33.9	+20.1	43.5	....	8.6
7/ 1	Theobromine sodium salicylate, 3 Gm. by mouth at 9:30 a. m.	9:30 a. m.	50	1.028	4.0	4.2	....	...	2.9	.....	4.5		
		12:00 noon	404	1.008	35.4	27.3	....	...	3.0	.....	4.0		
		2:00 p. m.	135	1.020	14.8	15.3	....	...	2.0	.....	6.6		
		4:30 p. m.	180	1.010	5.8	5.9	....	...	...	.....	3.9		
		6:30 p. m.	162	1.006	1.8	1.5	....	...	4.4	.....	4.1		
		9:00 p. m.	475	1.002	1.9	2.9	....	...	....	.....	6.2		
		7:00 a. m.	207	1.016	1.6	1.4	....	...	....	.....	13.8		
		Total.....	1,613	1.009	65.3	58.5	58.0	...	33.2	+10.8	43.1	....	8.9
7/ 2	.....	Total.....	1,763	1.008	55.6	53.8	41.2	...	29.4	+13.1	36.1	....	8.2
7/ 3	.....	Total.....	1,808	1.008	67.1	59.0	56.1	...	28.2	.....	36.3	....	7.4

* The valence was assumed to be 1.8.

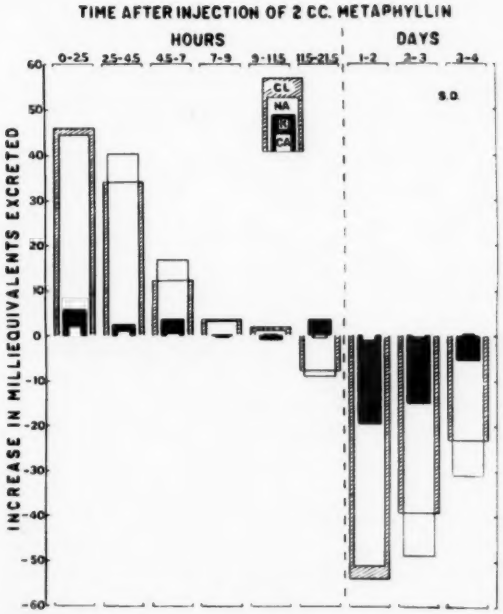

Fig. 2.—Net effect of the intravenous administration of 2 cc. of metaphyllin on the urinary excretion and subsequent retention of chloride, sodium, potassium and calcium in S. D.

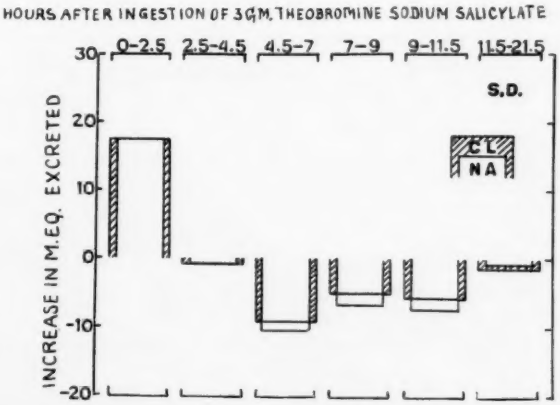

Fig. 3.—Net effect of the oral administration of 3 Gm. of theobromine sodium salicylate on the urinary excretion and subsequent retention of chloride and sodium in S. D.

derived from intracellular fluid. Since the potassium content of cell water is approximately 160 milliequivalents per liter, it is evident that little intracellular fluid was excreted by this subject following the administration of 2 cc. of merbaphen. Calculations of such small amounts inevitably contain a large inherent error, but it is interesting to note that the calculations for the excretion of potassium indicate the loss of approximately 60 cc. of cell water.

These calculations, on the basis of the amounts of sodium and potassium excreted, indicate that in this subject the predominant effect of merbaphen was a loss of extracellular fluid. The total calculated amount of water lost from the body, extracellular plus intracellular, was 1,090 cc. One might, therefore, expect an increase in the urinary volume and a net decrease in body weight of approximately the same amount; the observed increase in the volume of urine excreted during the diuretic period was 907 cc., and the net loss in weight [29] was 1,030 Gm. during the same period. There was considerable variation in the urinary volume during the corresponding periods of the three control days. With these considerations in mind, the correspondence between the calculated loss of body water and the increase in the urinary volume is satisfactory and supports the interpretation of the excretion of sodium and potassium during this diuresis in terms of loss of body fluid.

The minute amounts of calcium excreted in the urine during the control periods were increased several hundred per cent during the diuresis following merbaphen. The increased excretion of calcium during the diuretic period was, in this instance, 6 milliequivalents. Since the calcium content of normal interstitial fluid may be considered to be approximately 4 milliequivalents per liter,[30] and the diuresis in this instance was approximately 1 liter, it appears that the calcium excreted was derived mainly from the extracellular body fluids lost during the diuresis.

The increase in the amount of chloride excreted during the diuresis was approximately 6.8 Gm. or 190 milliequivalents. The total loss of body fluid during the diuresis, as calculated from the increased excretion of base, was 1,090 cc. If one assumes the chloride to be 110 milli-

29. The "net loss in body weight" refers to the loss of weight directly attributable to the effect of the drug, the factors of intake of food and water, blood drawn, stools excreted and average control urinary outputs and insensible losses of weight having been utilized in obtaining this value.

30. Loeb, R. F.; Atchley, D. W., and Palmer, W. W.: On the Equilibrium Condition Between Blood Serum and Serous Cavity Fluids, J. Gen. Physiol. **4**:591, 1922. Gilligan, Volk and Blumgart.[26] Greene, Bollman, Keith and Wakefield.[27]

equivalents per liter of water in body fluid [31] the excretion of chloride, to correspond to the excretion of base, was about 120 milliequivalents. This leaves an excess of 70 milliequivalents of chloride excreted which cannot be accounted for on the basis of loss of body fluid. Likewise, during the periods of retention following the diuresis (fig. 1) the chloride retained was in excess of the base retained. These findings will be discussed later.

Effect of 2 cc. of Metaphyllin Intravenously on S. D.—To compare the effect of the purine diuretics with that of the mercurial diuretics in the same subject, 2 cc. of metaphyllin [32] was injected intravenously. The intravenous method of administration was employed in order to render the results as comparable as possible. Metaphyllin caused a marked increase in the urinary output (table 3) and in the amounts of sodium, chloride, potassium and calcium excreted (fig. 2). The diuresis following the administration of metaphyllin lasted approximately nine hours. The periods of marked diuresis following metaphyllin coincided with those following merbaphen. The general relation between the various constituents excreted during the diuresis was similar in each period of marked diuresis. The period of retention following metaphyllin persisted for a somewhat shorter time (table 3); this is related to the fact that metaphyllin caused a smaller loss of constituents of the body fluids; consequently, under the fixed regimen of the study, a shorter period was required to restore these smaller amounts.

The increased amount of sodium excreted during the diuresis was approximately 2.3 Gm. or 100 milliequivalents; that of potassium, 0.46 Gm. or 12 milliequivalents, and that of calcium, 0.074 Gm. or 3.7 milliequivalents. According to the considerations previously discussed, calculations based on the increased amounts of sodium excreted gave a value of 690 cc. ($\frac{100 \text{ m.eq.}}{145 \text{ m.eq.}} \times 1{,}000$ cc.) for the extracellular fluid lost. The potassium content of this amount of extracellular fluid is approximately 3 milliequivalents. The remaining 9 milliequivalents of potassium excreted was presumably derived from intracellular fluid, as stated, and indicates the loss of approximately 60 cc. of cell water. Of the 3.7 milliequivalents of excess calcium excreted during the diuresis, approximately 2.8 milliequivalents can be accounted for on the basis of the calculated loss of water from the interstitial body fluids. The increase in the amount of chloride excreted during this diuresis was approxi-

31. This value may be assumed to be approximately correct for interstitial body water. Intracellular body water has a considerably smaller chloride concentration. Since the diuresis in this and in the following studies was mainly interstitial, this value serves as a close approximation. Footnote 30.

32. Two cubic centimeters of metaphyllin was diluted with 8 cc. of physiologic solution of sodium chloride when given intravenously.

mately 3.4 Gm. or 96 milliequivalents. According to the assumptions previously discussed, the amount of chloride excreted, to correspond to the amount of base excreted on the basis of body fluid contents, was 83 milliequivalents. The total calculated loss of body fluid during the nine hours of diuresis was 750 cc. Considering the inherent variations in the volume of urine on control days, this value compares satisfactorily with the observed increase of 874 cc. in the volume of urine and the net loss of body weight of 813 Gm. during this period. In S. D. the purine diuretic, metaphyllin, like merbaphen, exerted its effect predominantly on the extracellular fluids, the intracellular fluid compartment being affected to only a slight degree.

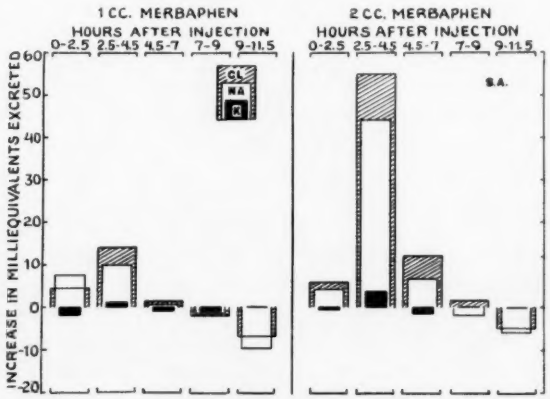

Fig. 4.—Net effect of the intravenous administration of 1 and 2 cc. of merbaphen on the urinary excretion of chloride, sodium and potassium in S. A.

Effect of 3 Gm. of Theobromine Sodium Salicylate Orally on S. D.—The oral administration of 3 Gm. of theobromine sodium salicylate caused a transitory diuresis (table 3) evident only in the first specimen of urine, which was voided two and a half hours after the drug had been given. The increased amounts of the inorganic ions excreted (fig. 3) were too small to permit making calculations of significance in regard to losses of body fluid. It should be noted that the retention of substances during the latter part of the twenty-four hour period during which the drug was given compensated fully for the amounts of chloride, sodium and water excreted in excess of the usual amounts. The total values for sodium, chloride and volume for the twenty-four hour period were consequently the same as on the days when no medication was given. The findings of some investigators who failed to observe any diuretic

effects after the administration of this drug [33] are readily understood, in view of the brief diuresis and the immediately ensuing retention observed by us, since these investigators measured only the total twenty-four hour specimens of urine.

Effect of 1 and 2 cc. of Merbaphen Intravenously on S. A.—To evaluate the effect of different doses of the same drug, 1 and 2 cc. of merbaphen were given to another subject (S. A.). An increase in the volume of the urine and in the amounts of sodium and chloride excreted occurred immediately after the intravenous administration of both 1 and 2 cc. of merbaphen (table 4). The relation of the increases in the various constituents of the urine (fig. 4) was similar to that noted in S. D. following 2 cc. of merbaphen, but much less striking. Two cubic centimeters of merbaphen was approximately three times as effective

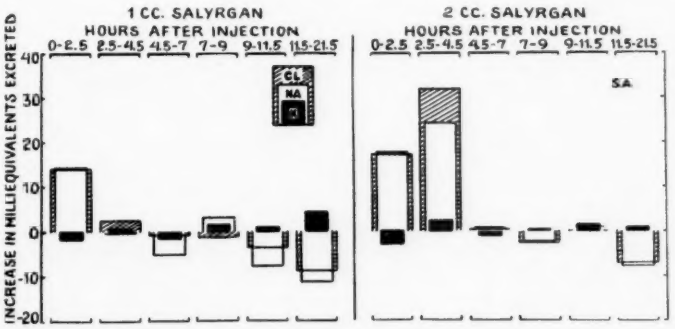

Fig. 5.—Net effect of the intravenous administration of 1 and 2 cc. of salyrgan on the urinary excretion of chloride, sodium and potassium in S. A.

as 1 cc., and the duration of the diuresis was somewhat longer. In this subject the urinary changes following merbaphen were not sufficiently great to warrant calculations of the amounts of intracellular and extracellular fluids represented by the increases in the urinary base, but the predominant loss of sodium indicates that the interstitial fluid compartment was drawn on mainly.

Effect of 1 and 2 cc. of Salyrgan Intravenously on S. A.—In this subject the diuretic effect of 2 cc. of salyrgan was somewhat less than that of 2 cc. of merbaphen (table 4). A twofold increase in the dose of salyrgan, i. e., from 1 to 2 cc., caused approximately a twofold increase in the duration of the diuresis and a threefold increase in the total output of water, sodium and chloride (fig. 5). The excretion of

33. Grossmann, M., and Sandor, J.: Zur klinischen Pharmakologie der Diuretika: I. Die Puringruppe, Wien. klin. Wchnschr. **38**:405, 1925.

TABLE 4.—*Effect of Diuretics on the Urinary Excretion of S. A.*

Date, 1931	Medication	Time of Voiding	Volume, Cc.	Specific Gravity	Chloride, M.Eq.	Sodium, M.Eq.	Potassium, M.Eq.	Calcium, M.Eq.	Ammonia Nitrogen, M.Eq.	Titratable Acidity Minus Carbon Dioxide, M.Eq.	Inorganic Phosphate Phosphorus,* M.Eq.	Inorganic Sulphate Sulphur, M.Eq.	Total Nitrogen, Gm.
4/ 3	.....	9:30 a. m.	72	1.024	8.4	5.5	6.6	...	2.9	+ 1.1	2.7		
		12:00 noon	223	1.012	17.0	10.4	11.4	...	2.4	— 2.1	1.3		
		2:00 p. m.	94	1.016	7.7	6.2	3.7	...	2.7	+ 2.0	3.2		
		4:30 p. m.	272	1.007	6.7	6.6	5.6	...	4.0	+ 1.3	3.7		
		6:30 p. m.	150	1.017	3.9	2.7	3.9	...	6.5	+ 2.7	4.1		
		9:00 p. m.	740	1.008	14.2	18.0	5.4	...	2.0	— 1.5	3.7		
		7:00 a. m.	256	1.022	7.5	14.9	9.7	...	...	+ 6.3	11.1		
		Total.....	1,807	1.013	65.4	64.3	46.2	...	...	+ 9.8	29.8		
4/ 6	.....	9:30 a. m.	98	1.015	8.6	5.4	9.2	...	5.8	+ 0.7	3.5		
		12:00 noon	330	1.005	18.2	10.9	12.2	...	0.4	— 2.4	1.7		
		2:00 p. m.	75	1.016	7.9	5.9	4.9	...	2.0	+ 1.9	3.1		
		4:30 p. m.	296	1.005	5.9	3.4	7.5	...	5.4	+ 2.1	3.7		
		6:30 p. m.	192	1.007	3.5	2.5	5.5	...	2.1	+ 2.7	4.3		
		9:00 p. m.†	207	1.008	5.8	6.7	5.4	...	2.2	+ 2.2	4.0		
		7:00 a. m.	512	1.009	10.3	7.4	12.9	...	11.2	+ 6.8	11.7		
		Total.....	1,710	1.010	60.2	42.2	57.6	...	29.1	+14.0	32.0		
4/ 7	Merbaphen, 1 cc. intravenously at 9:30 a. m.	9:30 a. m.	88	1.017	7.9	4.4	8.0	...	2.1	+ 1.2	3.5		
		12:00 noon	482	1.003	22.1	18.0	9.8	...	...	— 2.7	1.0		
		2:00 p. m.	122	1.011	21.9	16.0	5.3	...	2.4	+ 1.6	2.3		
		4:30 p. m.	430	1.005	7.9	5.6	5.7	...	3.1	+ 2.4	3.1		
		6:30 p. m.	70	1.018	1.7	1.2	3.4	...	2.8	+ 1.9	3.1		
		9:00 p. m.	230	1.008	3.2	2.8	5.4	...	4.3	+ 2.5	5.3		
		7:00 a. m.	350	1.011	7.0	3.1	15.7	...	13.8	+ 7.4	10.9		
		Total.....	1,772	1.008	71.7	51.1	53.3	...	....	+14.0	29.2		
4/ 8	.....	Total.....	1,711	1.008	49.9	39.6	52.8	...	26.5	+ 5.2	28.6		
4/ 9	.....	Total.....	1,821	1.009	67.7	73.3	46.4	...	27.1	+ 0.3	29.6		

5/16	.....	9:30 a. m.	70	1.019	6.3	4.8	5.1	...	....	.....	3.5		
		12:00 noon	380	1.005	14.8	10.6	10.0	...	....	.....	2.0		
		2:00 p. m.	70	1.020	8.6	6.5	4.4	3.8	....	.....	3.3		
		4:30 p. m.	155	1.012	9.5	5.9	8.1	...	....	.....	4.5		
		6:30 p. m.	145	1.011	3.9	4.4	3.1	...	....	.....	4.4		
		9:00 p. m.	445	1.013	5.6	6.6	3.2	...	....	.....	3.0		
		7:00 a. m.	360	1.015	20.6	23.9	15.8	...	....	.....	15.2		
		Total.....	1,625	1.013	69.3	62.7	49.7	...	....	.....	35.9	....	9.1
5/17	.....	9:30 a. m.	119	1.017	11.8	8.0	9.0	...	3.5	+ 0.8	4.4	5.1	
		12:00 noon	230	1.005	10.2	7.3	6.4	...	1.0	— 1.5	1.8	1.5	
		2:00 p. m.	75	1.016	7.8	6.7	4.5	2.5	2.6	+ 2.3	3.5	3.1	
		4:30 p. m.	345	1.005	10.4	7.5	8.2	...	7.2	+ 8.7	4.5	3.2	
		6:30 p. m.	215	1.007	6.1	6.9	5.8	...	3.7	+ 2.9	4.9	4.4	
		9:00 p. m.	512	1.004	11.1	14.2	7.5	...	2.3	— 1.8	4.2	3.6	
		7:00 a. m.	318	1.012	19.8	22.2	9.0	...	12.2	+ 5.1	13.5	12.2	
		Total.....	1,881	1.009	77.2	72.8	50.4	...	32.6	+16.5	36.8	33.1	9.1
5/18	.....	9:30 a. m.	80	1.013	8.7	6.7	6.0	...	2.2	+ 1.5	3.3	3.7	
		12:00 noon	395	1.004	25.8	24.6	8.6	...	2.5	— 5.0	1.4	3.8	
		2:00 p. m.	110	1.011	10.0	10.2	2.7	2.8	1.7	+ 1.7	3.1	2.5	
		4:30 p. m.	410	1.006	12.2	14.6	6.0	...	2.0	— 1.2	3.8	3.3	
		6:30 p. m.	85	1.018	4.7	4.6	5.1	...	3.2	+ 2.2	3.3	3.7	
		9:00 p. m.	416	1.006	8.2	7.4	7.7	...	3.7	+ 1.7	3.3	4.3	
		7:00 a. m.	304	1.016	10.6	7.5	19.5	...	13.2	+ 9.0	12.8	14.6	
		Total.....	1,800	1.009	80.2	75.6	55.6	...	28.3	+ 9.9	31.0	35.9	9.0
5/19	Merbaphen, 2 cc. intravenously at 9:30 a. m.	9:30 a. m.	65	1.021	5.3	4.0	6.1	...	2.8	+ 2.5	4.0	3.7	
		12:00 noon	382	1.004	22.6	18.3	7.8	...	3.0	— 1.2	1.4	3.1	
		2:00 p. m.	371	1.008	63.8	52.0	7.4	4.7	3.6	+ 2.0	2.8	2.3	
		4:30 p. m.	187	1.008	22.7	16.0	5.7	...	3.1	+ 1.9	2.7	2.6	
		6:30 p. m.	120	1.010	6.3	3.6	4.8	...	2.8	+ 1.9	2.6	2.8	
		9:00 p. m.	250	1.008	3.5	3.4	6.0	...	3.7	+ 2.8	5.3	4.2	
		7:00 a. m.	505	1.009	7.5	6.9	16.2	...	14.9	+10.0	17.4	12.8	
		Total.....	1,880	1.008	131.7	104.2	54.0	...	34.0	+19.9	35.7	31.5	8.9
5/20	.....	Total.....	1,627	1.007	30.3	34.0	37.1	...	34.2	+18.6	35.1	35.1	8.6
5/21	.....	Total.....	1,779	1.008	55.1	68.2	38.7	...	29.8	+ 9.6	30.8	....	8.5
5/22	.....	Total.....	1,500	1.009	62.9	58.9	41.5	...	28.3	+16.7	29.9	....	8.9

* The valence was assumed to be 1.8.
† Water scheduled for 7:30 p. m. was taken at 9:00 p. m.

TABLE 4.—*Effect of Diuretics on the Urinary Excretion of S. A.—Continued*

Date, 1931	Medication	Time of Voiding	Volume, Cc.	Specific Gravity	Chloride, M.Eq.	Sodium, M.Eq.	Potassium, M.Eq.	Calcium, M.Eq.	Ammonia Nitrogen, M.Eq.	Titratable Acidity Minus Carbon Dioxide, M.Eq.	Inorganic Phosphate Phosphorus,* M.Eq.	Inorganic Sulphate Sulphur, M.Eq.	Total Nitrogen, Gm.
5/23	.....	9:30 a. m.	114	1.018	13.3	10.8	7.0	...	....	.....	3.1		
		12:00 noon	515	1.007	18.3	14.5	11.8	...	....	.....	1.3		
		2:00 p. m.	124	1.015	12.1	10.4	5.3	...	....	.....	3.9		
		4:30 p. m.	420	1.005	11.7	11.0	8.6	...	....	.....	4.0		
		6:30 p. m.	92	1.016	5.3	4.7	5.3	...	....	.....	3.7		
		9:00 p. m.	520	1.005	5.4	7.4	5.8	...	....	.....	4.3		
		7:00 a. m.	260	1.017	10.1	7.1	17.0	...	....	.....	12.1		
		Total.....	2,045	1.008	76.2	65.9	60.8	...	41.3	+18.6	32.4	....	9 9
5/24	....	9:30 a. m.	205	1.007	11.0	7.4	9.4	...	....	.....	3.8		
		12:00 noon	300	1.004	15.4	12.1	9.4	...	....	.....	2.0		
		2:00 p. m.	130	1.015	12.8	13.0	3.9	...	....	.....	3.3		
		4:30 p. m.	425	1.005	14.2	13.5	6.9	...	....	.....	2.0		
		6:30 p. m.	155	1.008	6.2	6.3	4.1	...	....	.....	3.4		
		9:00 p. m.	440	1.005	10.1	16.4	4.5	...	....	.....	3.9		
		7.00 a. m.	335	1.013	16.4	18.2	14.0	...	....	.....	11.6		
		Total.....	1,990	1.008	86.1	86.9	52.2	...	....	.....	30.0	....	8.2
5/25	.....	9:30 a. m.	65	1.017	6.9	4.7	5.2	...	3.1	+ 2.4	3.3		
		12:00 noon	385	1.003	18.8	13.7	10.9	...	2.8	+ 7.3	2.3		
		2:00 p. m.	90	1.015	9.4	8.3	3.7	...	2.5	+ 1.9	3.6		
		4:30 p. m.	330	1.008	9.9	9.1	5.5	...	2.6	— 1.2	2.5		
		6:30 p. m.	97	1.010	4.5	3.8	4.6	...	3.3	+ 2.4	3.6		
		9:00 p. m.	462	1.003	7.7	9.4	5.7	...	3.1	+ 4.7	3.3		
		7:00 a. m.	235	1.015	11.8	10.6	13.4	...	13.7	+ 7.9	10.8		
		Total.....	1,664	1.008	69.0	59.6	49.0	...	31.1	+25.1	29.4	....	8.0
5/26	Metaphyllin, 2 cc. intramuscularly at 9:30 a. m.	9:30 a. m.	59	1.026	5.7	4.1	5.3	...	2.5	+ 2.3	3.3		
		12:00 noon	321	1.012	40.4	38.3	12.7	...	2.5	— 6.7	2.7		
		2:00 p. m.	183	1.011	18.2	18.4	5.3	...	2.4	+ 0.6	3.8		
		4:30 p. m.	357	1.008	12.3	12.3	8.3	...	2.6	— 0.2	3.9		
		6:30 p. m.	79	1.016	4.2	3.5	4.5	...	3.3	+ 3.0	4.6		
		9:00 p. m.	419	1.006	4.7	8.2	4.6	...	3.6	+ 1.5	5.5		
		7:00 a. m.	310	1.015	5.8	5.9	14.8	...	14.9	+ 9.3	15.0		
		Total.....	1,728	1.010	91.3	90.7	55.5	...	31.8	+ 9.8	38.8	....	8.7
5/27	.....	Total.....	1,720	1.008	43.2	35.4	46.3	...	32.0	+23.7	30.6	....	9.1
5/28	.....	Total.....	1,147	1.010	53.3	37.7	61.8	...	35.7	+21.8	31.4	....	8.3

6/ 1	.....	9:30 a. m.	115	1.014	9.9	7.8	6.2	...	....	+ 2.8	4.4		
		12:00 noon	332	1.008	17.1	12.9	12.1	1.1	....	— 2.1	2.1		
		2:00 p. m.	88	1.018	10.3	8.1	4.2	1.2	....	+ 2.3	3.5		
		4:30 p. m.	426	1.005	11.4	12.2	5.8	...	....	— 0.1	2.9		
		6:30 p. m.	177	1.010	6.6	8.6	3.6	...	....	+ 2.0	4.1		
		9:00 p. m.	395	1.006	6.0	10.5	3.7	...	....	+ 0.2	3.5		
		7:00 a. m.	413	1.012	16.2	18.6	12.3	...	....	+ 9.1	14.2		
		Total.....	1,946	1.009	77.5	78.7	47.9	...	....	+14.0	34.7		
6/ 2	.....	9:30 a. m.	63	1.021	6.5	5.0	4.3	0.6	....	+ 2.3	3.4		
		12:00 noon	400	1.006	18.4	14.2	10.4	1.5	....	— 2.6	1.5		
		2:00 p. m.	187	1.010	14.7	13.8	4.3	1.3	....	+ 2.2	4.3		
		4:30 p. m.	404	1.004	13.6	17.6	8.2	0.6	....	— 3.1	3.7		
		6:30 p. m.	290	1.007	8.2	9.8	4.6	0.7	....	+ 1.9	4.0		
		9:00 p. m.	430	1.008	9.7	14.6	4.5	0.5	....	— 0.4	3.8		
		7:00 a. m.	305	1.011	17.9	19.2	12.2	1.3	....	+ 7.5	13.0		
		Total.....	2,079	1.008	89.0	94.2	48.5	6.5	....	+ 7.8	33.7	....	8.8
6/ 3	Salyrgan, 1 cc. intravenously at 9:30 a. m.	9:30 a. m.	76	1.020	8.5	6.3	7.1	1.0	....	+ 3.2	4.0		
		12:00 noon	431	1.006	31.7	27.6	9.6	1.5	....	— 1.7	1.8		
		2:00 p. m.	183	1.008	14.9	10.7	4.9	1.1	....	+ 2.1	2.7		
		4:30 p. m.	320	1.007	11.6	9.7	5.4	0.6	....	+ 1.5	3.1		
		6:30 p. m.	182	1.008	6.1	12.4	5.6	0.4	....	+ 2.4	3.5		
		9:00 p. m.	264	1.005	4.3	4.6	5.2	0.3	....	+ 2.6	3.7		
		7:00 a. m.	422	1.010	8.2	7.4	16.6	1.0	....	+ 9.4	15.1		
		Total.....	1,878	1.009	85.3	78.7	54.4	5.9	....	+19.5	33.9	....	8.5
6/ 4	.....	Total.....	1,431	1.010	37.4	32.4	51.8	...	29.5	+21.5	32.4	....	8.4
6/ 5	.....	Total.....	1,906	1.008	68.5	67.2	56.5	...	27.6	+17.3	32.9	....	8.8
6/ 6	.....	Total.....	1,838	1.006	75.2	74.4	52.8	...	29.4	+15.8	32.9	....	8.6

* The valence was assumed to be 1.8.

TABLE 4.—*Effect of Diuretics on the Urinary Excretion of S. A.—Concluded*

Date, 1931	Medication	Time of Voiding	Volume, Cc.	Specific Gravity	Chloride, M.Eq.	Sodium, M.Eq.	Potassium, M.Eq.	Calcium, M.Eq.	Ammonia Nitrogen, M.Eq.	Titratable Acidity Minus Carbon Dioxide, M.Eq.	Inorganic Phosphate Phosphorus,* M.Eq.	Inorganic Sulphate Sulphur, M.Eq.	Total Nitrogen, Gm.
6/ 7	.....	9:30 a. m.	132	1.016	16.3	11.7	10.3	...	....	.....	3.3		
		12:00 noon	354	1.005	15.1	11.4	8.5	...	....	.....	1.4		
		2:00 p. m.	157	1.006	14.3	12.2	4.9	...	....	.....	3.4		
		4:30 p. m.	391	1.005	9.5	6.3	8.3	...	....	.....	3.5		
		6:30 p. m.	110	1.010	4.3	3.8	4.6	...	....	.....	3.8		
		9:00 p. m.	410	1.003	4.5	6.1	5.2	...	....	.....	3.0		
		7:00 a. m.	340	1.009	13.7	12.2	14.8	...	....	.....	12.0		
		Total.....	1,894	1.007	77.7	63.7	56.6	...	30.9	+18.0	30.4	....	8.9
6/ 8	.....	9:30 a. m.	84	1.019	8.3	6.4	6.6	...	....	.....	3.8	3.7	
		12:00 noon	198	1.011	13.6	7.3	11.3	...	....	.....	3.5	3.5	
		2:00 p. m.	107	1.013	5.8	3.9	5.3	...	....	.....	4.5	2.3	
		4:30 p. m.	348	1.005	7.2	4.9	7.3	...	....	.....	4.1	3.7	
		6:30 p. m.	339	1.005	5.7	6.0	4.8	...	....	.....	4.1	3.5	
		9:00 p. m.	484	1.005	9.8	16.2	5.3	...	....	.....	5.3	5.0	
		7:00 a. m.	351	1.013	16.0	18.5	14.1	...	....	.....	14.6	14.8	
		Total.....	1,911	1.009	66.4	63.2	54.7	...	30.2	.....	39.9	36.5	9.3
6/ 9	.....	9:30 a. m.	150	1.012	15.0	7.6	7.0	...	3.1	.....	3.5	3.2	
		12:00 noon	460	1.006	22.8	20.3	12.4	...	2.3	.....	1.9	2.9	
		2:00 p. m.	137	1.011	10.8	9.6	3.9	...	2.6	.....	3.4	2.5	
		4:30 p. m.	628	1.006	18.2	16.8	8.6	...	3.1	.....	3.4	3.0	
		6:30 p. m.	250	1.005	7.8	9.1	3.2	...	3.3	.....	3.3	3.5	
		9:00 p. m.	360	1.004	6.3	9.9	5.8	...	2.7	.....	4.9	4.4	
		7:00 a. m.	380	1.011	14.6	15.9	15.3	...	13.8	.....	16.0	12.8	
		Total.....	2,265	1.007	95.5	89.4	56.2	...	30.9	.....	36.4	32.3	9.2
6/10	Salyrgan, 2 cc. intravenously at 9:30 a. m.	9:30 a. m.	91	1.016	8.8	7.2	5.4	1.0	3.0	.....	4.7	3.2	
		12:00 noon	361	1.008	34.2	30.6	7.6	1.6	3.1	.....	1.6	2.4	
		2:00 p. m.	261	1.010	42.3	32.8	7.1	1.8	3.3	.....	1.7	2.4	
		4:30 p. m.	370	1.006	11.8	10.1	7.0	0.6	2.8	.....	3.3	2.8	
		6:30 p. m.	180	1.008	3.0	3.9	4.5	0.4	3.3	.....	3.3	3.3	
		9:00 p. m.	490	1.006	6.9	11.7	6.9	0.8	3.1	.....	4.6	4.3	
		7:00 a. m.	337	1.010	8.3	8.0	15.4	0.7	13.2	.....	12.8	15.0	
		Total.....	2,090	1.008	115.3	104.3	53.9	6.9	31.8	.....	32.0	33.4	9.5
6/11	.....	Total.....	1,899	1.008	53.4	56.0	45.3	...	27.6	.....	35.7	34.5	9.4
6/12	.....	Total.....	1,823	1.008	60.8	56.9	50.7	...	29.7	.....	37.6		
6/13	.....	Total.....	1,955	1.009	58.6	....	58.3	...	30.8	+13.7	35.6	....	9.1
6/14	.....	Total.....	2,328	1.007	98.7	....	63.2	...	31.2	+11.3	39.2	....	9.6

* The valence was assumed to be 1.8.

potassium was not significantly altered. The relation between the excretion of sodium and that of chloride in this subject was qualitatively the same as that following merbaphen in S. D. As observed following the other diuretics, the predominant excretion of the base sodium indicates that the diuresis following salyrgan represents fluid drawn mainly from the interstitial spaces.

Effect of 2 cc. of Metaphyllin Intramuscularly on S. A.—The diuresis following the intramuscular injection of 2 cc. of metaphyllin (table 4) appeared as promptly as it did in the other subjects after intravenous administration and persisted for four and a half hours after the injection (fig. 6). In this patient the diuretic effect was significantly less

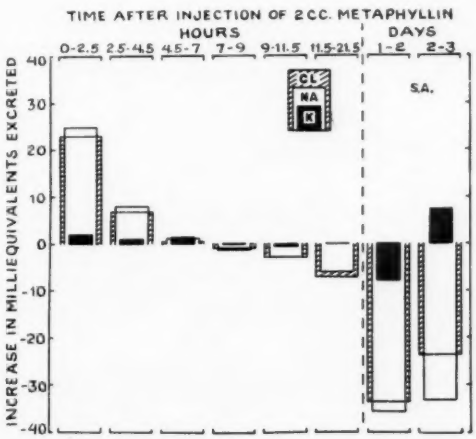

Fig. 6.—Net effect of the intramuscular administration of 2 cc. of metaphyllin on the urinary excretion and subsequent retention of chloride, sodium and potassium in S. A.

than that caused by 2 cc. of the mercurial diuretics, salyrgan and merbaphen. The relation between the various inorganic ions excreted was similar to that observed in S. D. following 2 cc. of metaphyllin.

Effect of Two Doses of 2 cc. of Metaphyllin Intravenously on E. W.—The intravenous injection of 2 cc. of metaphyllin on two separate occasions caused an increase in the volume of urine during the first eleven and a half hours after administration in both instances (table 5). The relation between the increased amounts of inorganic ions excreted (figs. 7 and 8) was approximately that observed in S. D. and S. A. following 2 cc. of metaphyllin. During the diuresis on the first occasion, the following increases were noted: sodium, 53; chloride, 41; potassium, 5,

TABLE 5.—*Effect of Diuretics on the Urinary Excretion of E. W.*

Date, 1931	Medication	Time of Voiding	Volume, Cc.	Specific Gravity	Chloride, M.Eq.	Sodium, M.Eq.	Potassium, M.Eq.	Calcium, M.Eq.	Ammonia Nitrogen, M.Eq.	Titratable Acidity Minus Carbon Dioxide, M.Eq.	Inorganic Phosphate Phosphorus,* M.Eq.	Inorganic Sulphate Sulphur, M.Eq.	Total Nitrogen, Gm.
10/17	.....	9:30 a. m.	64	1.016	4.0	5.3	2.0	0.2	....	.....	1.9		
		12:00 noon	71	1.017	3.9	5.9	2.0	0.3	....	.....	2.5		
		2:00 p. m.	93	1.014	3.5	6.0	2.0	0.5	....	.....	3.6		
		4:30 p. m.	200	1.010	6.0	10.4	2.8	0.3	....	.....	4.1		
		9:00 p. m.	331	1.011	9.1	19.5	3.7	0.5	....	.....	6.9		
		7:00 a. m.	855	1.010	43.9	57.8	10.7	1.1	....	.....	11.4		
		Total.....	1,614	1.011	70.4	104.9	23.2	2.9	13.1	+ 5.2	30.4	34.2	8.8
10/18	.....	9:30 a. m.	74	1.017	6.1	7.2	1.5	0.3	....	.....	2.6		
		12:00 noon	133	1.014	6.7	10.5	2.1	0.4	....	.....	3.3		
		2:00 p. m.	52	1.018	3.1	4.9	1.3	0.2	....	.....	2.5		
		4:30 p. m.	146	1.015	7.3	12.4	3.8	0.3	....	.....	4.8		
		9:00 p. m.	370	1.011	9.8	20.0	4.1	0.4	....	.....	6.9		
		7:00 a. m.	612	1.011	29.8	38.9	9.3	0.9	....	.....	10.5		
		Total.....	1,387	1.012	62.8	93.9	22.1	2.5	14.0	+10.2	30.6	35.1	8.7
10/19	.....	9:30 a. m.	82	1.015	5.7	7.3	2.4	0.3	....	.....	2.7		
		12:00 noon	130	1.011	5.7	8.7	2.1	0.4	....	.....	3.3		
		2:00 p. m.	116	1.011	3.8	6.7	1.6	0.3	....	.....	3.5		
		4:30 p. m.	130	1.010	3.6	6.8	1.5	0.2	....	.....	3.0		
		9:00 p. m.	360	1.009	9.3	19.2	4.0	0.6	....	.....	7.8		
		7:00 a. m.	785	1.008	38.8	49.0	11.6	1.1	....	.....	11.7		
		Total.....	1,633	1.009	66.9	97.7	23.2	2.9	12.1	+10.1	32.0	33.7	8.9
10/20	Metaphyllin, 2 cc. intravenously at 9:30 a. m.	9:30 a. m.	102	1.017	8.2	10.0	3.9	0.4	....	.....	3.1		
		12:00 noon	265	1.012	22.2	30.8	2.8	1.2	....	.....	3.4		
		2:00 p. m.	142	1.015	12.4	17.4	2.9	0.5	....	.....	3.7		
		4:30 p. m.	113	1.015	9.8	13.4	2.7	0.3	....	.....	2.8		
		9:00 p. m.	534	1.010	20.9	35.5	7.2	0.6	....	.....	9.2		
		7:00 a. m.	600	1.009	27.8	34.6	8.5	0.6	....	.....	8.4		
		Total.....	1,756	1.010	101.3	141.7	28.0	3.6	12.2	+ 2.2	30.6	34.2	9.2
10/21	.....	Total.....	1,352	1.011	51.2	74.7	21.9	2.4	14.1	+14.1	28.7	35.2	9.0
10/22	.....	Total.....	1,359	1.010	50.1	76.8	19.1	3.3	15.0	+11.5	31.4	....	9.2
10/23	.....	Total.....	1,555	1.012	63.3	94.5	22.6	3.2	14.1	+ 7.1	31.7	....	9.2
10/24	.....	Total.....	1,663	1.011	69.5	100.5	24.0	3.3	15.6	+ 7.3	29.0	....	9.2

10/31	.....	9:30 a. m.	84	1.015	5.8	7.3	2.5	0.4					
		12:00 noon	133	1.009	4.2	6.7	1.5	0.5					
		2:00 p. m.	102	1.014	4.5	7.2	1.7	0.5					
		4:30 p. m.	239	1.010	6.6	13.1	2.5	0.5					
		9:00 p. m.	380	1.010	9.2	20.1	3.6	0.7					
		7:00 a. m.	650	1.010	35.8	45.4	9.7	1.3					
		Total.....	1,588	1.010	66.1	99.8	21.5	3.9	16.3	.....	24.5	....	8.7
11/ 1	.....	9:30 a. m.	84	1.016	7.8	9.2	3.1	0.4					
		12:00 noon	60	1.016	3.4	4.9	1.6	0.4					
		2:00 p. m.	92	1.017	5.3	8.6	2.2	0.5					
		4:30 p. m.	221	1.010	7.1	13.4	2.8	0.4					
		9:00 p. m.	493	1.007	8.9	19.3	3.9	0.6					
		7:00 a. m.	503	1.010	32.3	37.5	10.7	1.1					
		Total.....	1,453	1.009	64.8	92.9	24.3	3.4	....	.....	27.9	....	8.6
11/ 2	.....	9:30 a. m.	94	1.016	8.3	9.1	4.6	0.4					
		12:00 noon	146	1.012	5.8	9.1	2.3	0.5					
		2:00 p. m.	141	1.011	5.5	8.4	2.5	0.3					
		4:30 p. m.	255	1.007	5.0	9.4	1.9	0.5					
		9:00 p. m.	314	1.010	7.6	15.5	3.1	0.5					
		7:00 a. m.	597	1.010	25.2	32.6	9.7	1.0					
		Total.....	1,547	1.009	57.4	84.1	24.1	3.2	18.7	+ 9.7	29.3	....	8.4
11/ 3	Metaphyllin, 2 cc. intravenously at 9:30 a. m.	9:30 a. m.	90	1.015	6.6	7.1	3.4	0.4					
		12:00 noon	479	1.008	29.4	37.7	4.2	1.6					
		2:00 p. m.	261	1.010	15.7	21.4	3.4	0.9					
		4:30 p. m.	207	1.011	11.8	18.3	3.4	0.4					
		9:00 p. m.	492	1.010	16.8	31.8	4.6	0.6					
		7:00 a. m.	298	1.014	16.4	22.0	7.4	0.5					
		Total.....	1,827	1.010	96.7	138.3	26.4	4.4	13.5	— 3.3	30.2	....	9.1
11/ 4	.....	Total.....	996	1.013	32.2	56.1	19.7	3.6	15.8	+11.3	22.8	....	7.9

* The valence was assumed to be 1.8.

and calcium, 1.2 milliequivalents. On the second occasion the increases were: sodium, 64; chloride, 50; potassium, 6.3, and calcium, 1.4 milliequivalents. These amounts are less than those observed in S. D. following the intravenous administration of 2 cc. of metaphyllin. However, the variations on control days were slight (table 5), and the relative response in the four individual periods of diuresis on each occasion was so constant (figs. 7 and 8) that calculations concerning the loss of body fluid are significant. With the considerations outlined, the calculated loss of body fluid represented by the increases in urinary sodium and potassium during the diuresis on the first occasion was approximately 370 cc. for extracellular and 20 cc. for intracellular fluid, making a total of 390 cc. The chloride content of this amount of body fluid is approximately 43 milliequivalents, which compares well with the actual excess excretion of 41 milliequivalents of urinary chloride. The calcium content of this amount of body fluid is approximately 1.5 milliequivalents and is significantly similar to the actual excess urinary excretion of 1.2 milliequivalents. The increase in urinary volume observed during the diuresis was 425 cc. as compared to the calculated loss of 390 cc. of body fluid. Likewise, on the second occasion, the amount calculated for the extracellular fluid was approximately 440 cc. and that for the intracellular fluid, 30 cc., making a total of 470 cc. The chloride content of this amount of body fluid is approximately 52 milliequivalents, which compares well with the observed increased excretion of 50 milliequivalents of urinary chloride. The calcium content could be expected to be 1.9 milliequivalents, which is comparable to the observed excretion of 1.4 milliequivalents. The increase in urinary volume observed during the diuresis on this occasion was 580 cc. as compared with the calculated loss of 470 cc. of body fluid. The degree of correspondence of all these calculated and observed values is surprisingly close when one considers the pitfalls which may be encountered in the study of water and salt metabolism. After the diureses caused by metaphyllin in E. W., as in all other instances, there followed a compensating retention of water and salts (table 5).

Urinary Output of Inorganic Phosphate, Inorganic Sulphate, Total Nitrogen, Ammonia and Titratable Acid and Specific Gravity of the Urine During Diuresis.—No significant changes in the urinary excretion of inorganic phosphate could be detected following the administration of any of the mercurial or xanthine diuretics studied. Keith and Whelan [34] likewise found no significant changes in the twenty-four hour urinary output of inorganic phosphate following the administration

34. Keith, N. M., and Whelan, M.: A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, J. Clin. Investigation **3**:149, 1926.

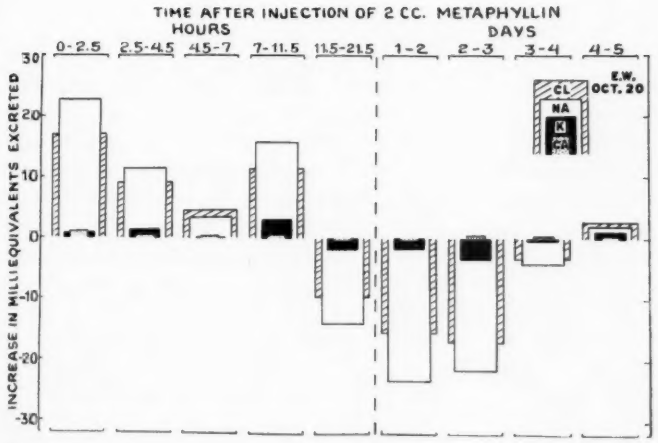

Fig. 7.—Net effect of the intravenous administration of 2 cc. of metaphyllin on the urinary excretion and retention of chloride, sodium, potassium and calcium in E. W.

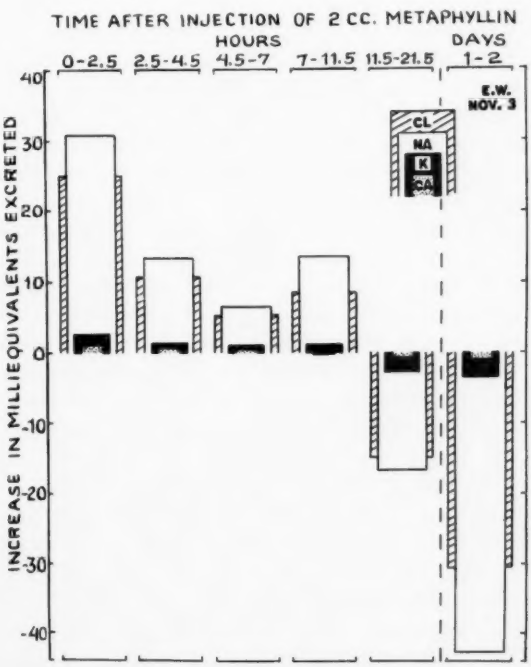

Fig. 8.—Net effect of the intravenous administration of 2 cc. of metaphyllin on the urinary excretion and retention of chloride, sodium, potassium and calcium in E. W. Figure 8 is to be compared with figure 7 which also shows the effect of 2 cc. of metaphyllin in this subject on another occasion.

of 2 cc. of merbaphen in normal men. Other investigators[35] have found a decrease in the excretion of inorganic phosphate during the diureses caused by metaphyllin and theobromine sodium salicylate, while an increased excretion has been observed during the diureses caused by sodium nitrate, sodium chloride, sodium sulphate and urea.[36] The absence of appreciable changes in the excretion of inorganic phosphate during the diureses observed in our studies is consistent with the concept that the effect of the diuretics studied is mainly to cause a loss of body water with its constituent inorganic ions. The amount of inorganic phosphate in 1 liter of normal interstitial fluid is approximately from 2 to 3 milliequivalents. The largest diuresis observed in the aforementioned studies (S. D. following 2 cc. of merbaphen) was approximately 1 liter. Even in this instance the added amount of urinary inorganic phosphate which one might expect to be excreted on this basis (from 2 to 3 milliequivalents) could not be detected accurately under the conditions of the study, since the output of inorganic phosphate in the control periods, corresponding to the nine-hour period of diuresis, varied by this amount. The important fact is, therefore, that beyond these limits no changes in the excretion of phosphate were observed following either the mercurial or the xanthine diuretics studied.

The excretion of inorganic sulphate was studied in divided periods following the administration of 2 cc. of merbaphen, 2 cc. of salyrgan and 2 cc. of metaphyllin (tables 3, 4 and 5). The excretion of inorganic sulphate during diuresis did not differ appreciably in any instance from that in the control periods. This finding is consistent with the fact that inorganic sulphate is present in extremely small amounts in normal body fluids.

Measurements of the output of total nitrogen in the urine were made for periods of twenty-four hours throughout the studies. The output of total urinary nitrogen was not affected in any of the studies (tables 3, 4 and 5).

Studies of the urinary excretions of titratable acid (minus carbon dioxide) and of ammonia during the aforementioned diureses corroborated certain of the other findings. In all the studies following the administration of mercurial diuretics, with the exception of observations on S. D. following 2 cc. of merbaphen, the additional excretions of fixed acid (chloride) and fixed base constituents (sodium, potassium and calcium) were so nearly the same that no change in titratable acidity or ammonia was anticipated, and none was found. In S. D. following 2 cc. of merbaphen the excess chloride excreted during the diuresis

35. Bolliger, A.: The Influence of the Purine Diuretics on Inorganic Phosphates of Blood and Urine, J. Biol. Chem. **76**:797, 1928.

36. Hendrix, B. M., and Calvin, D. B.: The Loss of Bases in Diuresis and Its Effect upon the Alkali Reserve of the Blood, J. Biol. Chem. **65**:197, 1925.

exceeded the sum of the amounts of sodium, potassium and calcium [37] excreted by approximately 20 milliequivalents. The urinary excretion of ammonia was slightly increased, the titratable acidity remaining within the limits of the control variations (table 3).

In E. W. on the two occasions following metaphyllin, the ammonia and titratable acidities were measured for periods of twenty-four hours. The excretion of ammonia was not affected. The titratable acidity (minus carbon dioxide) decreased appreciably on both of the days of diuresis. This finding is in accord with the fact that the excess excretions of fixed base exceeded those of fixed acid in amounts closely approximating those for normal interstitial body fluids. (The bicarbonate or "volatile acid" of normal interstitial fluid is approximately 30 milliequivalents per liter.[26]) In S. D. following 2 cc. of metaphyllin the excretion of ammonia did not differ significantly from that on control days; the titratable acidity was not measured. In S. A. the excretion of ammonia following 2 cc. of metaphyllin did not differ significantly from that on control days. The titratable acidity tended to be lower than on most of the control days, although on control days the variation of titratable acidity was such that interpretation must be guarded. The apparent lowering of the titratable acidity is in harmony with the observations on E. W. following 2 cc. of metaphyllin.

According to the concept that the increased urinary excretion following the diuretics studied represents definite volumes of body fluids, the specific gravity of the excess fluid excreted during the diuresis would be approximately 1.009, a value representative of protein-free interstitial fluid. In each period of diuresis the increased amount of urine excreted constituted but a part of the entire specimen of urine, the specific gravity of which was measured. Consequently one would expect the specific gravity of each specimen (during the periods of diuresis) to be closer to 1.009 than during analogous control periods. The variations in the specific gravity of the urine during the control periods were relatively great, so that an exact evaluation of the specific gravities of the additional fluids excreted during the diuresis is not possible in these studies. In cases with pathologic conditions with edema, to be reported later, in which the specific gravities of the urine were more constant on control days and the volume of diureses greater than those observed in this study, the specific gravity of the excess fluid excreted during the diuresis, as calculated from the specific gravities and volumes for control periods and periods of diuresis, was demonstrated to be close to 1.009.

37. The excretion of magnesium was not determined in any of the experiments but probably the increase amounted to not more than 3 milliequivalents during any diuresis.

Effect of Diuretics on the Excretion of Water and Salt in the Stools.—Since appreciable amounts of water and inorganic salts are normally excreted in the stools, it seemed necessary, in a complete study of the effects of the diuretics on the water and salt metabolism, to learn to what extent the fecal excretion of these substances was affected by the drugs. The stools collected during certain periods when no medication was given were analyzed for their content of water, sodium, chloride, potassium, phosphorus and calcium, and the results were compared with those obtained when diuretics were being administered (table 6). The fecal excretion representing periods of diuresis is necessarily calculated from three day periods, although the drug was administered on only one of these days. This method is the most satisfactory one available and should reveal any important change in fecal excretion during the

TABLE 6.—*Analyses of Stools*

Subject	Period	Date When Period Began	No. of Days in Period	Medication*	Water, Gm. per Day	Chloride, M.Eq. per Day	Sodium, M.Eq. per Day	Potassium, M.Eq. per Day	Calcium, M.Eq. per Day	Phosphorus, M.Eq. per Day
S. D.	1	3/22/31	4	None	81	3.7	0.4	5.9	12.5	10.4
	2	3/26/31	3	None	66	2.3	1.3	7.1	15.0	9.2
	3	3/29/31	3	None	68	3.1	2.6	6.4	14.0	10.9
	4	4/ 1/31	3	None	97	4.2	1.3	11.5	15.5	14.4
	5	5/22/31	3	Merbaphen, 2 cc.	88	4.2	1.3	11.2	17.5	14.4
	6	6/ 9/31	3	Metaphyllin, 2 cc.	104	3.4	...	8.4	19.5	16.7
S. A.	1	3/22/31	6	None	47	2.0	0.9	7.9	....	18.4
	2	3/28/31	4	None	99	3.1	2.6	11.5	....	26.4
	3	4/ 1/31	6	None	55	2.5	1.3	7.9	....	17.8
	4	4/ 7/31	3	Merbaphen, 2 cc.	62	4.2	2.2	15.1	....	18.4
	5	5/19/31	3	Merbaphen, 2 cc.	63	3.4	1.7	10.2	....	17.3
	6	5/26/31	3	Metaphyllin, 2 cc.	98	4.5	1.3	10.2	....	23.0
	7	6/10/31	3	Salyrgan, 2 cc.	60	3.4	0.4	10.2	....	29.8

* All the drugs were given on the first day of the period.

period of diuresis. If there were, for instance, an increase of more than approximately 0.1 Gm. of sodium or 0.3 Gm. of chloride during the diuresis, the retention during the remainder of the three day period in which the stools were examined could not possibly be entirely compensatory, even though no sodium or chloride was excreted during this time (table 6).

The amounts of water and inorganic constituents in the stools representing periods during which diuretics were given did not differ appreciably from the amounts of these substances present when no drugs were administered (table 6). No toxic gastro-intestinal effects were noted clinically except in S. A. during period 5 (table 6). He experienced moderate abdominal cramps during the first twelve hours after 2 cc. of merbaphen, and on that day passed four small stools of normal consistency. These findings indicate that, under conditions similar to those of this study, in the absence of diarrhea it is unnecessary to include an examination of the stools in evaluating the effect of diuretics on the water and salt metabolism.

Effect of Diuretics on the Insensible Loss of Water.—As shown by Wiley and his co-workers,[38] studies of water metabolism involve: four sources of intake, namely, the water drunk, water in food, water of oxidation and preformed water; and three sources of elimination, namely, urine, stools and insensible perspiration. The common clinical method of using the water drunk and the urinary water excreted as an index of change in water balance in the body is valid only for comparatives changes when all the other stated factors remain relatively constant.

To determine whether in normal persons the increase of water in the urine following the administration of diuretics under the conditions of our experiments is an accurate measure of the increased loss of water from the body, it is necessary first to determine to what extent the diuretics cause changes in the other paths of elimination, namely, the stools and the insensible perspiration. It has been shown that the various diuretics caused no appreciable changes in the amount of water secreted in the stools. This factor, therefore, need not be taken into account in evaluating comparative losses of water from the body in control periods and in periods of diuresis.

The insensible loss of weight has been studied in S. D. and S. A. (table 7) during control periods and during similar periods following the administration of diuretics. For purposes of comparison, calculations have been made for the periods including the four and a half hours from 9:30 a. m. to 2 p. m., the routine schedule (table 1) including dinner at 12 noon being adhered to as usual. In each instance the subjects remained in bed in a sitting or lying posture. The room temperature was not above 78 F., the humidity relatively constant, and the activity of the subjects controlled for the experimental periods. The diuretic was administered in each case at 9:30 a. m., and the greatest diuresis always occurred between that time and 2 p. m. Consequently whatever changes occurred in insensible loss of water coincident with an increase in urinary output during the diuresis would be apparent in this period.

The following considerations are necessary for the interpretation of the data: The total insensible loss is calculated from the following formula: insensible loss of weight = weight at 9:30 a. m. — (weight at 2 p. m. — ingesta + urine + stool + blood drawn). The insensible loss of weight is the resultant of the weight of the insensible water lost, the weight of the carbon dioxide exhaled and the weight of the oxygen absorbed.[38b] Expressed as an equation in which the weight of each substance is employed: insensible loss of weight = $H_2O + (CO_2 - O_2)$.

38. (*a*) Wiley, F. H., and Newburgh, L. H.: The Relationship Between the Environment and the Basal Insensible Loss of Weight, J. Clin. Investigation **10**:689, 1931. (*b*) Newburgh, L. H.; Wiley, F. H., and Lashmet, F. H.: A Method for the Determination of Heat Production Over Long Periods of Time, ibid. **10**:703, 1931.

The (CO_2—O_2) factor is a function of the metabolic mixture utilized by the patient and amounts to a small portion of the total loss, which portion may be considered constant under the conditions of our studies. The changes in total insensible loss of weight therefore represent a measure of the changes in the insensible loss due to water. In S. D. the insensible loss was determined for three control periods from 9:30 a. m. to 2 p. m. and gave an average of 89 Gm. per hour. Similarly, determinations made after the administration of 2 cc. of merbaphen, 3 Gm. of theobromine sodium salicylate and 2 cc. of metaphyllin averaged

TABLE 7.—*Insensible Loss of Water During the First Four and a Half Hours Following Diuretics Compared to Similar Periods When no Diuretics Were Administered*

Subject	Date	Medication	Insensible Loss of Weight (9:30 a. m. to 2:00 p. m.) Gm. per Hour
S. D.	5/21/31	None	114
	5/22/31	Merbaphen, 2 cc.	93
	5/23/31	None	66
	6/ 9/31	Metaphyllin, 2 cc.	80
	6/10/31	None	75
	6/29/31	None	74
	6/30/31	None	79
	7/ 1/31	Theobromine sodium salicylate, 3 Gm.	63
S. A.	4/ 3/31	None	39
	4/ 6/31	None	50
	4/ 7/31	Merbaphen, 1 cc.	46
	4/ 8/31	None	38
	5/18/31	None	38
	5/19/31	Merbaphen, 2 cc.	43
	5/20/31	None	51
	5/25/31	None	42
	5/26/31	Metaphyllin, 2 cc.	49
	5/27/31	None	71
	6/ 2/31	None	32
	6/ 3/31	Salyrgan, 1 cc.	35
	6/ 9/31	None	33
	6/10/31	Salyrgan, 2 cc.	37
	6/11/31	None	52

79 Gm. per hour. Comparative figures for periods during which there was a retention of sodium, chloride and water following the diureses caused by merbaphen and metaphyllin averaged 71 Gm. per hour.

In S. A. the insensible loss was determined on six control days and averaged 39 Gm. per hour. The results of similar determinations made following the administration of 1 and 2 cc. of merbaphen, 1 and 2 cc. of salyrgan and 2 cc. of metaphyllin averaged 42 Gm. per hour. The results of determinations made on four different days during the periods of retention following diuresis gave an average insensible loss of 52 Gm. per hour.

The variability in the total insensible loss for the four and a half hour periods studied was considerable on control days. This same

observation was made by Wiley and Newburgh [38a] who cited the difficulties of determining complete water balances over short periods of time. The fluctuations in the volume of urine during the aforementioned individual periods of control days were not significantly dependent on these relatively minor fluctuations in insensible loss of water.

The various diuretics produced no significant effect on the insensible loss of water during the periods of diuresis or retention. The variability in the amount of the insensible loss of water during the periods of diuresis and retention was similar to that of the control periods.

TABLE 8.—*Effect of Diuretics on the Serum of Normal Persons*

Subject	Medication	Date	Hour	Chloride, M.Eq. per Liter	Sodium, M.Eq. per Liter	Specific Gravity
S. D.	Metaphyllin, 2 cc. at 9:30 a. m.	6/ 9/31	9:25 a. m.	101	142	1.0272
			11:10 a. m.	99	142	1.0274
			12:25 p. m.	98	138	1.0274
			1:40 p. m.	99	138	1.0276
S. A.	None.....	4/ 6/31	9:25 a. m.	98		
			10:05 a. m.	99		
			12:00 noon	100		
			2:00 p. m.	98		
	Merbaphen, 1 cc. at 9:30 a. m.	4/ 7/31	9:25 a. m.	99		
			10:05 a. m.	99		
			12:00 noon	99		
			2:00 p. m.	98		
	Salyrgan, 1 cc. at 9:30 a. m.	6/ 3/31	9:25 a. m.	99	142	1.0271
			11:25 a. m.	100	142	1.0265
			12:25 p. m.	101	142	1.0262
			1:40 p. m.	100	142	1.0265
		6/ 4/31	9:40 a. m.	100	...	1.0271
	None.....	6/29/31	9:25 a. m.	100	145	1.0269
			11:25 a. m.	100	144	1.0263
			12:25 p. m.	99	145	1.0264
			1:40 p. m.	100	145	1.0265
E. W.	None.....	11/2/31	9:25 a. m.	97	137	1.0256
			12:00 noon	96	136	1.0243
	Metaphyllin, 2 cc. at 9:30 a. m.	11/3/31	9:25 a. m.	96	137	1.0257
			12:00 noon	97	137	1.0259

These findings lead to the conclusion that the effect of diuretics in normal persons can be evaluated without introducing calculations of the insensible loss of water, provided the conditions of room temperature, humidity and activity of the subject are controlled as they were in these studies.

Effect of Diuretics on Serum Constituents.—The results of repeated analyses of the blood serum for sodium, chloride and specific gravity at intervals before, during the height of and after the diuresis did not differ appreciably from those obtained at similar times on control days (table 8). Since the urinary analyses showed that the increased excretions during these periods of diureses, in which hematologic studies were made (table 8), were of the approximate composition of body fluids, one would not expect a measurable change in the concentrations of the serum

electrolytes studied in these instances. Keith and Whelan [34] analyzed the blood of normal subjects for various constituents before, and approximately six and twenty-four hours after, the administration of merbaphen. No constant changes were observed, but in the absence of measurements of the urine during the first few hours after the administration of the drug the significance of their results is not clear. In S. D., calculations of the nature of the fluid excreted during the diuresis following 2 cc. of merbaphen showed the excretion of chloride to be somewhat in excess of that expected on the basis of the chloride composition of a volume of body fluid equal to the volume excreted during the diuresis. Analyses of serum were not made in this instance. Since the total amount of urine excreted during the period of diuresis was approximately 1 liter, it seems possible that a slight measurable lowering of the serum chloride concentration might have been detected. In a series of cases of pathologic edema, to be reported later, in which salyrgan and merbaphen caused diureses of from 1 to 5 liters, analyses of the serum chloride usually showed appreciable decreases (amounting to as much as 10 milliequivalents in one instance), and the serum bicarbonate showed closely compensatory increases. The serum base was unchanged. The reported hematologic observations following diuretics in pathologic conditions have been adequately reviewed by Schmitz.[39]

Effect of Diuretics on the Rate of Glomerular Filtration and Tubular Reabsorption.—According to the current concept of renal function the increased excretion of water and certain inorganic ions following diuretics may be accomplished by an increase in glomerular filtration or by a decrease in tubular reabsorption, these changes being either absolute or relative. To estimate the relative importance of these two factors during the diuresis we have measured the rate of glomerular filtration and of tubular reabsorption according to the method of Rehberg,[22] slightly modified (table 9). The validity of the Rehberg test as a measure of the rate of glomerular filtration is not universally accepted. Even though the method may contain absolute errors, relative changes before and during the diuresis may still provide insight into the action of the diuretics. The technic used differed from that described by Rehberg in that no creatinine was fed and the Folin method of measurement of creatinine [23] was employed. It seemed inadvisable to feed creatinine in these studies since its effect on water and salt metabolism is not established. The modified method employed was satisfactory for our purposes. Check analyses of the same samples of blood serum and of urine showed good agreement. The values for serum creatinine varied somewhat from day to day in the

39. Schmitz, H. L.: The Effect of Euphyllin and Salyrgan upon Glomerular Filtration and Tubular Reabsorption, J. Clin. Investigation **11**:1075, 1932.

TABLE 9.—*Effect of Diuretics on the Rate of Glomerular Filtration and on Tubular Reabsorption* *

			9:30 a. m. to 12 Noon					12 Noon to 2 p. m.				
Subject	Date	Medication	Rate of Glomerular Filtration, Cc. per Minute	Reabsorbed Fluid, per Cent of Filtered	Urea Clearance, per Cent of Normal	Volume of Urine, Cc. per Minute	Output of Chloride, Gm.	Rate of Glomerular Filtration, Cc. per Minute	Reabsorbed Fluid, per Cent of Filtered	Urea Clearance, per Cent of Normal	Volume of Urine, Cc. per Minute	Output of Chloride, Gm.
S. D.	5/21/31	None	106	99.2	.....	0.94	0.97	97	98.8	.....	1.19	0.53
	5/22/31	Merbaphen, 2 cc.	119	97.4	.....	3.06	2.64	85	95.3	.....	4.02	3.52
	6/ 9/31	Metaphyllin, 2 cc.	91	95.6	95 (M)	4.02	2.16	95	96.5	126 (M)	3.20	1.54
	7/ 1/31	Theobromine sodium salicylate, 3 Gm.	80	96.6	110 (M)	2.68	1.25	80	98.6	138 (S)	1.12	0.53
S. A.	5/18/31	None	65	96.0	.....	2.63	0.92	53	98.3	.....	0.92	0.36
	5/19/31	Merbaphen, 2 cc.	60	95.8	.....	2.54	0.80	61	94.9	.....	3.10	2.27
	5/25/31	None	67	96.2	.....	2.57	0.67	68	98.9	.....	0.75	0.34
	5/26/31	Metaphyllin, 2 cc.	75	97.0	.....	2.21	1.43	66	97.7	.....	1.52	0.65
	6/ 3/31	Salyrgan, 1 cc.	69	95.8	.....	2.88	1.13	70	97.8	.....	1.52	0.53
E. W.	11/2/31	None	52	96.1	.....	1.02	0.21	55	98.3	.....	1.04	0.20
	11/3/31	Metaphyllin, 2 cc.	57	94.1	.....	3.40	1.04	59	96.5	.....	2.06	0.56
J. S.	10/6/32	None	73	99.4	99 (S)	0.39	0.22					
	10/7/32	Metaphyllin, 2 cc.	75	93.9	86 (M)	4.65	2.28					
B. E.	10/7/32	None	50	97.4	77 (S)	1.35	0.55					
	10/5/32	Metaphyllin, 2 cc.	67	94.4	92 (M)	3.79	2.12					

* All the drugs were given at 9:30 a. m.
(M) refers to maximum and (S) to standard urea clearances.

same subject, but repeated analyses at different times on a given day during the periods studied showed that the value for serum creatinine was constant. The values found probably include other chromogenic substances besides creatinine, but for the comparative purposes of this study such a limitation does not seem important. These considerations are corroborated by studies in two additional subjects in whom the amount of creatinine in the blood was increased by creatinine feeding to approximately 6 mg. per hundred cubic centimeters. In these instances the results before and during the diuresis lead to the same interpretation of the effects of the diuretics as in the instances in which creatinine was not fed.

The rate of glomerular filtration as measured by the creatinine clearance was not altered significantly during periods of marked diuresis following either the xanthine or the mercurial diuretics (table 9). The volume of urine excreted per minute and the excretion of chloride during the diuresis were at times several hundred per cent greater than during control periods and bore no relation to changes in the rate of glomerular filtration. In S. D., for instance, the rate of glomerular filtration on the day when no medication was given was 106 cc. per minute during the period from 9: 30 a. m. to 12 noon, and the volume of urine was 0.9 cc. per minute. During similar periods following 2 cc. of metaphyllin and 3 Gm. of theobromine sodium salicylate the rates of glomerular filtration were 91 and 80 cc. per minute and the volumes of urine, 4 and 2.7 cc. per minute, respectively (table 9).

These results indicate that the diuresis observed in our subjects cannot be attributed to changes in the rate of glomerular filtration. Values for urea clearance following diuretic drugs were also obtained in certain instances (table 9), and the findings are in agreement with this concept.

The amount of tubular reabsorption has been calculated by subtracting the volume of urine in cubic centimeters per minute from the rate of glomerular filtration in cubic centimeters per minute. To reduce our results to a comparable basis, the tubular reabsorption has been expressed in percentage of the rate of glomerular filtration for each period. A decrease in the percentage of tubular reabsorption was observed in every instance during the diuresis. Similar calculations on the basis of the amounts of sodium and chloride present in the serum and urine show that the tubular reabsorption of sodium and chloride is likewise reduced following the administration of these diuretics. These observations indicate that in normal subjects the increased excretion of water and salts by the kidneys, following the diuretics studied, is accomplished by a relative decrease in the tubular reabsorption of these substances. Likewise Schmitz,[39] in experiments on dogs, and

Herrmann and his co-workers,[40] in studies on patients with cardiac edema, have shown that the mercurial diuretics cause a decrease in the percentage of tubular reabsorption with no significant effect on the rate of glomerular filtration. These authors, however, found significant increases in the rate of glomerular filtration following metaphyllin. The conditions under which these results were obtained differed in important respects from those employed in our studies. Since Schmitz gave to dogs the same amount of metaphyllin as we administered to our subjects, the dosage in his experiments was proportionately many times greater. The dosage of metaphyllin employed by Herrmann was also larger than the usual clinical dose used by us, and his studies were made on patients with cardiovascular disease. Under these conditions this drug may act in a different manner. Our results, which indicate that in normal persons the diureses following both the mercurial and the xanthine diuretics cannot be attributed to increases in rates of glomerular filtration, are in harmony with those obtained in normal subjects by Chrometzka and his co-workers [41] and by Gavazzeni,[42] who used the usual Rehberg method with the feeding of creatinine.

COMMENT

There are certain points in common to all the aforementioned studies of the water and salt metabolism in normal subjects following the administration of both the xanthine and the mercurial diuretics: 1. The output of water, sodium, chloride, potassium and calcium is increased after the diuretics (fig. 9). 2. The increases in water and in the bases—sodium, potassium and calcium—bear a constant relation to each other; the data indicate that the fluid lost from the body during diuresis was derived mainly from the interstitial body compartment. 3. There is no significant change in the phosphate, sulphate, ammonia or total nitrogen metabolism. 4. The increases in the excretion of water and fixed base in the urine following the various diuretics represent the loss of equivalent volumes of body fluids with their basic constituents. 5. The water and salts lost from the body of these subjects with normal water balances during the diuresis are regained by a compensatory retention. 6. There is no significant change in the insensible loss of water or in the water or salt content of the stools.

40. Herrmann, G.; Stone, C. T., and Schwab, E. H.: Some Studies on the Mechanism of Diuresis in Patients with Congestive Heart Failure, Tr. A. Am. Physicians **47**:279, 1932.

41. Chrometzka, F., and Unger, K.: Untersuchungen über die Grösse des Glomerulusfiltrats unter dem Einfluss von Diureticis und Hormonen, Ztschr. f. d. ges. exper. Med. **80**:261, 1931.

42. Gavazzeni, M.: Filtrato glomerulare e diuretici, Policlinico (sez. med.) **39**:236, 1932.

7. In the instances reported no significant changes were observed when repeated analyses of the blood serum for sodium, chloride and specific gravity were made at intervals before, during the height of, and after, the diuresis. 8. Measurements of the rate of glomerular filtration and tubular reabsorption according to the method of Rehberg, somewhat modified, indicate that the increased excretion of water and salts is accomplished by a relative decrease in tubular reabsorption, the rate of glomerular filtration remaining unaffected.

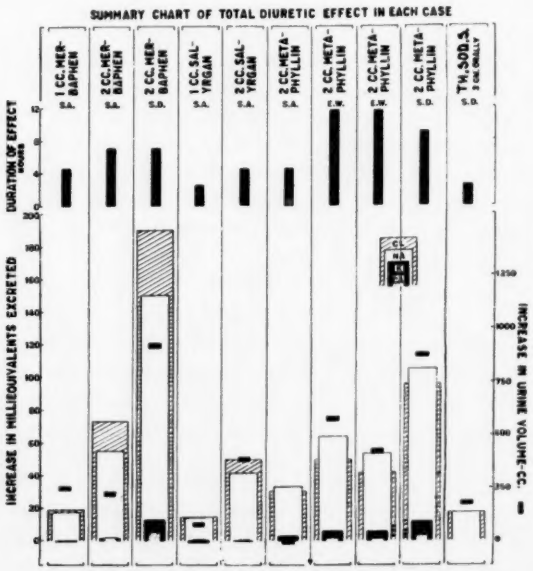

Fig. 9.—Summary of the net effect of the diuretic drugs on the duration of diuresis and on the excretion of water, chloride, sodium, potassium and calcium.

The output of chloride following the xanthine diuretics compared well with that expected from the loss of body fluid as calculated on the basis of the losses of water and fixed base. Following the mercurial diuretics, the excretion of chloride was somewhat greater than that expected. Corresponding with these findings the titratable acidity was decreased following the xanthine and unchanged following the mercurial diuretics.

These considerations show that in general the effect of the different diuretics studied is qualitatively the same, the essential difference being in the magnitude and duration of the effect. A general comparison of the magnitude and duration of the effect of the various diuretics in our

subjects (fig. 9) reveals reasons for the many discrepancies between the results reported in the literature. Previous studies have been concerned mainly with a comparison of the effect of diuretics in different patients who have shown considerable variation in their clinical state, or they have been confined to the effect of one type of diuretic on the twenty-four hour specimens of urine of normal persons. Under the standard conditions employed in the present investigation, examination of the numerous specimens of urine has shown that the mercurial and xanthine diuretics have a general relation to each other in regard to their potency in the same subject. The mercurial diuretics, merbaphen and salyrgan, were more effective than the xanthine diuretics, metaphyllin and theobromine sodium salicylate, when the usual clinical dose was administered. This relation was present consistently in each subject (fig. 9). The period of maximum diuresis generally occurred during the first two and a half hours following the xanthine, and between two and a half and four and a half hours following the mercurial diuretics. The general level of response to all the diuretics was greater in one subject than in another. S. D. showed a greater response to merbaphen than S. A., and a greater response to metaphyllin than either S. A. or E. W. This variation in response to the same diuretic in different subjects emphasizes the value of comparative studies in the same person. The difference in response shown by various subjects may be related to body size. The largest response to a given diuretic was always observed in the largest subject (S. D.), in whom the total amount of body fluids available for excretion was presumably the greatest. Although the size of the kidneys may also be an important factor, the same relation between the magnitude of the diuresis and the amount of body fluid available for excretion has also been observed by us in pathologic conditions with edema; i. e., in a patient with edema the diuretic effect of a drug decreases as the patient becomes less edematous. Further, the work of Lie [43] indicates that in a normal subject the diuretic response to caffeine is increased when isotonic salt solution is administered previous to the diuretic. The duration of the effect of the diuretics, likewise, showed considerable variability from person to person, although, in general, the magnitude and duration of effect were directly related to one another.

In comparing the effects of the diuretics there is an underlying assumption that under strictly comparable conditions in the same person a given amount of a drug produces a closely similar effect on different occasions. To test the validity of this assumption, the same amount of metaphyllin was given to E. W. on two separate occasions when his condition by all available tests seemed the same. Both times the responses were in satisfactory agreement in regard to the relation between the

43. Lie, E.: Caffein and Diuresis in Man, Am. J. Physiol. **92**:619, 1930.

various constituents and the absolute amounts excreted. Similarly, when different doses of the same diuretic were given to the same subject there was a definite relation between the amount of the dose and the magnitude and duration of the response. Doubling the dose approximately doubled the duration of the effect and trebled the magnitude of the diuresis.

Throughout this investigation repeated examinations of the urine were made for albumin, casts and cellular elements. No evidences of possible irritative renal effects were observed. Except for vomiting after 4 Gm. of theobromine sodium salicylate by mouth in the same subject and for abdominal cramps, but no watery diarrhea, after 2 cc. of merbaphen, no toxic effects were noted after any of the diuretics.

As shown previously in this communication, the proportions of the individual bases in the extra amounts of fixed base excreted during the diuresis were the same as those in the body fluids, and these bases were excreted with an extra volume of water which, in general, conformed to the expected amount of body fluid.

These considerations indicate that the diuretics cause an excretion of definite volumes of body fluids. The increase in the fixed bases excreted in the urine during diuresis is the base content of the body water lost. This finding reflects the obstinacy with which the organism maintains the constancy of the total electrolyte concentration of its internal environment and is a further illustration of homeostasis.[44] These results of the action of diuretics are analogous to the observations of Gamble and his co-workers [24] in studies of the metabolism of a fasting subject and furnish strong support for his interpretation of the urinary excretion in his subject in terms of body fluids. The calculations of the relative percentages of intracellular and extracellular water excreted indicate that the source of the body water excreted was almost entirely extracellular, the intracellular amounts being only 10 per cent or less of the total. While such calculations are inevitably only approximations, they are in accord with the concept of the importance of the lability of the extracellular body fluids in maintaining the constancy of the volume of intracellular fluids. This is suggested not only by the smaller amounts of intracellular fluid excreted, as indicated by the excretion of potassium (fig. 9), but also by the fact that the excretion of intracellular fluid tended to be greater after the initial withdrawal of considerable amounts of extracellular fluids (figs. 1 and 2). This action of the mercurial and xanthine diuretics in liberating more readily the extra-

44. Cannon, W. B.: The Wisdom of the Body, New York, W. W. Norton & Company, 1932.

cellular water in the body is similar to the action of the acid-producing salts in the patients studied by Gamble and his co-workers.[45]

The amounts of water and salts retained during the periods following diuresis consistently amounted to somewhat more than the amounts lost during that period (figs. 1, 2 and 6). This slight overcompensation was followed by a secondary excess output immediately following, which resulted in the restoration of the original store of body water. This phenomenon of overcompensation is often encountered in the study of physiologic mechanisms. The compensatory retention of substances lost during diuresis in normal subjects is in marked contrast to the course of events following the dissipation of edema with diuretics in pathologic conditions.

To gain information regarding the mechanism of diuresis in our subjects, studies of the blood for sodium, chloride and specific gravity were repeatedly made at intervals before, during the height of, and after, the diuresis. The negative results of these studies are opposed to the opinions of investigators who believe that diuresis following diuretic drugs is initiated by the kidneys in response to measurable changes in the blood. Our results are in accord with the theory that a loss of the various inorganic ions and of water by the blood stream is immediately compensated by an influx from extravascular sources. The considerations discussed earlier in this communication indicate that the sources of this extravascular fluid are predominantly extracellular and to only a slight extent intracellular.

Experiments to elucidate the nature of the action of the various diuretics on the human kidney are difficult to design. Assuming the validity of the considerations underlying the determination of the rate of glomerular filtration by the method of Rehberg, our studies show that in normal subjects neither the mercurial nor the xanthine diuretics studied have an effect on the rate of glomerular filtration but cause an increase in the amount of urine and its constituents by a relative decrease in tubular reabsorption.

CONCLUSIONS AND SUMMARY

1. Eleven studies on three normal subjects were undertaken in order to define more accurately the nature and mechanism of the action of diuretics.

2. Four different diuretics were administered: salyrgan and merbaphen of the mercurial group, and metaphyllin and theobromine sodium salicylate of the xanthine group. The relationship between the amount of the drug given and the magnitude of the diuretic response was studied.

45. Gamble, J. L.; Blackfan, K. D., and Hamilton, B.: A Study of the Diuretic Action of Acid Producing Salts, J. Clin. Investigation **1**:359, 1925.

3. The regimen employed afforded sufficient constancy of water and salt metabolism of the body to evaluate the effects of medication. A constant uniform diet and the same measured amounts of water were given at specified times every day throughout these studies. Likewise, specimens of urine were collected at specified times at short intervals during the day.

4. All the diuretics studied caused an increased output of water, sodium, chloride, potassium and calcium. No significant change occurred in the metabolism of phosphate, sulphate, ammonia or total nitrogen.

5. Interpretation of the results on the basis of the salt content of body fluids has been made to gain information as to the source of the increased output of water and inorganic salts following the administration of the diuretics. The relation between the increased amounts of water, sodium, potassium and calcium excreted after a diuretic is approximately the same as that existing in the body fluids. The increased amount of chloride excreted during the periods of diuresis after the xanthine diuretics is likewise approximately the same as that existing in an equivalent amount of body fluid; after the mercurial diuretics the excretion of chloride is somewhat greater.

6. Analysis of the amounts of sodium and potassium excreted on the basis of the concentrations in which they exist in the extracellular and intracellular fluids shows that the diureses represented a predominant loss of extracellular body fluids, the intracellular loss being only 10 per cent or less of the total.

7. The increased amounts of calcium in the urine during diuresis are mainly derived from the body fluids excreted.

8. The water and salts lost from the body in normal subjects during diuresis were regained by a compensatory retention which began immediately on the cessation of diuresis. On the constant dietary regimen employed, the greater the diuresis, the longer was the time necessary for the body to regain its lost fluid.

9. A relationship was evident between the magnitude of the diuretic response and the amount of body fluids available for excretion; i. e., the greatest diuretic response to a given drug was observed in the largest subject.

10. In general, merbaphen produced a slightly greater effect than the same amount of salyrgan; the xanthine diuretics caused a smaller response than a comparable clinical dose of the mercurial diuretics.

11. Doubling the dose of salyrgan and of merbaphen approximately doubled the duration of the diuresis and approximately trebled its magnitude.

12. Neither the xanthine nor the mercurial diuretics caused measurable changes in the specific gravity or in the sodium or chloride contents of the blood serum during the height of, or after, diuresis in these normal subjects. The negative results of these studies are opposed to the opinions of investigators who believe that diuresis following diuretic drugs is initiated by the kidneys in response to measurable changes in some of these constituents in the blood.

13. The rate of glomerular filtration, measured by the method of Rehberg (modified), appeared to be the same during the diureses caused by both the mercurials and the xanthines as it was on the control days. This suggests that the diureses observed in our subjects were not related to changes in the rate of glomerular filtration.

14. The percentage of tubular reabsorption, on the other hand, was always found to be decreased, and the decrease was in proportion to the diuretic effect.

15. The diuretic effects of the various drugs studied were qualitatively similar, the differences being in magnitude and duration rather than in kind.

JERUSALEM ARTICHOKE IN THE TREATMENT OF DIABETES

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The purpose of the experiments was to determine whether the carbohydrate contained in Jerusalem artichoke is more available for the nutrition of certain subjects with severe diabetes than equal quantities of other carbohydrates. Feeding experiments were carried out with two human subjects with severe diabetes and with a completely phlorhizinized dog.

DIABETIC SUBJECTS

CASE 1.—R. P., a man, aged 38 years, first had symptoms of diabetes at the age of 29 years. The disease had run a rapid course, and to the date of the experiments the patient had had a quantitative diet with insulin for seven years. During this time he had been continuously under the observation of Dr. R. T. Woodyatt, and was an intelligent, trained and experienced patient. His usual diet contained carbohydrate 105, protein 127 and fat 183, on which he remained in good health, but not free from morning glycosuria on an insulin dose of 75 units.

CASE 2.—H. E., a man, aged 49 years, had had diabetes since the age of 40 and had required treatment with insulin for seven years. This patient was very intelligent and a trained and experienced patient who had been under Dr. R. T. Woodyatt's observation continuously for seven years. His customary diet contained carbohydrate 94, protein 74 and fat 181, with calories 2,301 and an estimated dextrose equivalent of 155 Gm.,[1] on which the urine was usually free from sugar with an insulin dosage of 50 units, divided into 40 in the morning and 10 in the evening.

JERUSALEM ARTICHOKE

The product used consisted of dried slices of the tuber Helianthus tuberosus. The product was analyzed for carbohydrate by hydrolysis, reduction and polariscopy; for total nitrogen by the Kjehldahl method; for fat by desiccation and extraction by ether, and for water by desiccation and total ash by weight after combustion. Total protein was estimated as 6.25 × total nitrogen. The data obtained are shown in table 1.

Levulose.—Weighed parts of the desiccated product weighing from 1 to 20 Gm. were hydrolyzed with from 200 to 500 cc. of 0.9 per cent hydrochloric acid at water-bath temperature. During the process samples of the hydrolysate were

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This investigation was financed by Pabst Dietary Products Inc., of Milwaukee.

From the Department of Medicine of Rush Medical College of the University of Chicago and Presbyterian Hospital.

1. The D, or available dextrose, was calculated by the formula: $D = C + 0.58\ P + 0.1\ F$.

drawn off and analyzed at intervals of fifteen minutes to determine the time at which the reducing power had reached a maximum. The maximum was usually reached at the end of two hours and a half, before which hydrolysis was incomplete and after which darkening of the fluid and loss of reduction showed the destruction of some carbohydrate. The hydrolysate was cooled rapidly and was exactly neutralized to litmus while in an ice bath. The portion to be used for polariscopy was cleared with blood charcoal. The reducing power was determined by modification of the Folin colorimetric method for the determination of sugar in the blood. The hydrolysates were always strongly levorotatory. The levorotation and reducing power expressed in terms of levulose are shown in table 2.

TABLE 1.—*Analysis of Jerusalem Artichoke*

Analysis	Carbohydrate, per Cent	Protein, per Cent	Fat, per Cent	Water, per Cent	Ash, per Cent	Fiber and Undetermined Constituents, per Cent
1	68.2	7.2	0.5	4.0	5.9	....
2	68.9	7.4	0.5	...	5.8	....
3	69.9	7.3	...	...	...	....
4	69.5	...	...	...	...	....
5	67.4	...	...	...	...	....
6	67.9	...	...	...	...	....
7	70.0	...	...	...	...	....
8	68.6	...	...	...	...	....
9	68.6	...	...	...	...	....
Average	68.8	7.3	0.5	4.0	5.8	13.6

TABLE 2.—*Levulose in Hydrolysates of Jerusalem Artichoke*

Analysis	Levulose by Reduction, Gm.	Levulose by Polariscopy, Gm.
1	5.46	2.0
2	5.51	2.4
3	5.59	2.1
4	5.56	2.2
5	5.39	2.1
6	5.43	2.2
7	5.60	2.0
8	5.49	2.1
9	5.49	2.1
Average	5.50	2.1

As both the levorotation and reducing power disappeared after fermentation with yeast it appeared that a large portion of the reducing substance was levulose. The hydrolysate always gave a strong test for ketoses.

EXPERIMENTS

Experiment 1.—*Phlorinized Dog.*—After a dog, weighing 11.5 Kg., had fasted for twenty-four hours, the animal was given 1 Gm. of phlorizin subcutaneously every twenty-four hours during the experiment, which was carried out in eight hour periods. Deglycogenization was accomplished with 0.04 cc. of epinephrine hydrochloride in a 1:1,000 dilution, per kilogram, given every four hours, until the dextrose-nitrogen ratio became constant. The results of the first six periods are shown in table 3.

In periods 3, 4 and 5 the dextrose-nitrogen quotient was constant at an average of 3.03, giving a glycogenic factor for protein for this dog of 3.03/6.25, or 0.48. During those three periods 32.2 Gm. of dextrose was excreted. Allowing for this caloric loss, the animal was given one sixth of its basal caloric requirements as half milk and half 22 per cent cream every four hours.

At the beginning of the fifteenth period the feedings were changed in an attempt to bring about a nitrogen equilibrium. In periods 8 to 12, 107 calories in the form of dextrose was lost in the urine each twenty-four hours. At this time the animal weighed 10.25 Kg. The nitrogen excreted in periods 10 to 12 was 7.8 Gm. Allowing 30 calories per kilogram above the urinary loss of calories as dextrose and adding sufficient casein to give 7.8 Gm. of nitrogen each twenty-four hours, the twenty-four hour feeding requirement was calculated as 57 Gm. of 33 per cent

TABLE 3.—*Results of Deglycogenization of Dog During First Six Periods*

Period	Feeding	Dextrose in Urine, Gm.	Nitrogen in Urine, Gm.	D/N
1	0	15.23	1.8	8.46
2	0	10.62	3.1	3.43
3	0	10.40	3.5	2.97
4	0	11.12	3.7	3.00
5	0	11.64	3.7	3.11
6	0	12.80	3.6	3.52

TABLE 4.—*Results of Deglycogenization of Dog During Seventh to Fourteenth Periods*

Period	Feeding: ½ Cream, ½ Milk, Gm.	Dextrose in Urine, Gm.	Nitrogen in Urine, Gm.	D/N
7	48 48	15.51	3.4	4.56
8	Same as 7	12.54	3.1	4.04
9	Same as 7	12.43	2.8	4.44
10	Same as 7	10.80	2.7	4.00
11	Same as 7	9.95	2.6	3.82
12	Same as 7	11.54	2.5	4.56
13	Same as 7	10.53	2.4	4.39
14	Same as 7	9.16	2.5	3.66

cream and 52 Gm. of casein. Fifty-nine cubic centimeters of 33 per cent cream was diluted with water to exactly 300 cc. To 50 cc. of this diluted cream 8.66 Gm. of casein was added, and the mixture was fed every four hours without difficulty.

In periods 17 to 19, or the three periods preceding the feeding of Jerusalem artichoke, the average amount of dextrose excreted per period was 12.35 Gm. and the average amount of nitrogen was 3.7 Gm. while the average dextrose-nitrogen quotient was 3.32. It will be noted that the diet of cream and casein stabilized the excretion of dextrose and nitrogen.

In period 20, 10 Gm. of pulverized dry slices of Jerusalem artichoke were added to each of two feedings.

In period 20, the extra dextrose from artichoke was $15.23 - (3.5 \times 3.32) = 3.61$ Gm.; in period 21, $17.39 - (3.9 \times 3.32) = 4.44$ Gm.; in period 22, $13.93 - (3.8 \times 3.32) = 1.31$ Gm., making the total extra dextrose excreted 9.36 Gm.

The specimens of urine from periods 20, 21 and 22 were dextrorotatory, and the dextrose value determined polariscopically agreed with that calculated from

reduction determinations. The reducing substance was fermented by yeast. The average amount of dextrose excreted in each of periods 23, 24 and 25, or the three periods following the feeding of Jerusalem artichoke, was 12.25 Gm., and the average amount of nitrogen was 3.5 Gm. The theoretical quantity of dextrose available from 20 Gm. of Jerusalem artichoke as calculated from the formula was: $D = C + 0.48\ P + 0.1\ F. = 72.4 \times 0.20 = 14.48$ Gm. The percentage of the theoretical available dextrose obtained as extra dextrose was $9.36/14.48 \times 100$, or 64.6 per cent. This figure is comparable to those obtained by Sansum and Woodyatt,[2] who found that from 52 to 75 per cent of the feeding was extra dextrose when quantities of from 8 to 16 Gm. of pure dextrose were fed.

TABLE 5.—*Feedings of Dog to Establish Nitrogen Equilibrium*

	Feeding		Dextrose in Urine, Gm.	Nitrogen in Urine, Gm.	D/N
Period	Cream Mixture, Cc.	Casein, Gm.			
15	50 50	8.66 8.66	11.69	3.2	3.64
16	Same as 15		12.02	3.7	3.25
17	Same as 15		12.19	3.7	3.27
18	Same as 15		12.19	3.7	3.27
19	Same as 15		12.65	3.7	3.42

TABLE 6.—*Excretions of Dog During and Following Feeding of Jerusalem Artichoke*

	Feeding			Dextrose in Urine, Gm.	Nitrogen in Urine, Gm.	D/N
Period	Cream Mixture, Cc.	Casein, Gm.	Jerusalem Artichoke, Gm.			
20	50 50	8.66 8.66	10 10	15.23	3.5	4.35
21	50 50	8.66 8.66	0 0	17.39	3.9	4.46
22	Same as 21			13.93	3.8	3.66
23	Same as 21			12.29	3.6	3.41
24	Same as 21			12.36	3.5	3.53
25	Same as 21			12.09	3.4	3.56

Experiment 2.—Diabetes Mellitus (case 1).—The patient, weighing 69 Kg., was receiving a diet of carbohydrate 82, protein 74 and fat 179, with D 143 and calories 2,233. Thirty-two units of insulin before breakfast, 16 units before the evening meal and 4 units at 3 a. m. permitted a slight glycosuria during the entire twenty-four hours, without acidosis. This diet and the insulin were used in all of the control periods. During the feeding periods oatmeal or Jerusalem artichoke, each calculated to produce 23 Gm. of available dextrose, was added to this diet, but the dosage of insulin was kept constant. Insulin from the same batch was used during the entire experiment. To make sure that the daily collections of urine were complete, creatinine determinations were made on each twenty-four hour specimen by the method using picramic acid. The urinary dextrose was determined by the Folin-Berglund method and checked by polariscopy, and the total nitrogen was determined by the Kjeldahl process.

2. Sansum, W. D., and Woodyatt, R. T.: J. Biol. Chem. **24**:23, 1916.

The average amount of dextrose in the urine for the period preceding the special feedings was 10.62 Gm., and that of nitrogen, 9.3 Gm. Oatmeal calculated to give 23 Gm. of available dextrose and 0.8 Gm. of nitrogen was added to the diet. The dextrose in the urine rose to an average of 11.27 Gm. and the nitrogen to 10.5 Gm. The oatmeal was then removed from the diet and the average amount of dextrose in the urine dropped to 6.76 Gm. and that of nitrogen to 10 Gm. During the period when oatmeal was in the diet the average daily increase in the amount of urinary dextrose above the average of the fore and after periods was 2.58 Gm.

The average amount of dextrose excreted in the urine during the period preceding the feeding of Jerusalem artichoke was 9.09 Gm., and that of nitrogen was 11 Gm. Jerusalem artichoke calculated to give 23 Gm. of available dextrose was added to the diet. The average daily excretion of dextrose rose to 13.66 Gm. and the nitrogen to 11.3 Gm.

The daily specimens of urine during this period were dextrorotatory, and the dextrose value determined polariscopically agreed with that calculated from reduction determinations. The reducing substance was fermented by yeast.

The artichoke was then removed from the diet, and the average amount of dextrose in the urine dropped to 8.21 Gm. and that of nitrogen remained at 11.3 Gm. The average daily increase in the urinary dextrose while artichoke was included in the diet was 5.01 Gm. It will be noted that the average amount of dextrose excreted in the periods preceding and following the experiment with oatmeal was 8.69 Gm. and in the experiment with artichoke 8.65 Gm.

Experiment 3.—*Diabetes Mellitus* (case 2).—The patient, weighing 60 Kg., was receiving a diet of carbohydrate 92, protein 54 and fat 172, with D 141 Gm. and calories 2,132. Thirty-six units of insulin taken before breakfast and 16 units before the evening meal permitted a slight glycosuria during the entire twenty-four hours, without acidosis. Insulin from the same source as that of experiment 2 was used. The experiment was carried out by the same procedure used in experiment 2.

The average amount of dextrose in the urine before the special feedings was 9.42 Gm. and that of nitrogen 8.2 Gm. While oatmeal was included in the diet the average amount of dextrose in the urine rose to 17.06 Gm. and that of nitrogen to 8.7 Gm. In the period following, the average excretion of dextrose was 7.66 Gm. and that of nitrogen 7.9 Gm. The increase in the amount of urinary dextrose when oatmeal was fed was 8.52 Gm.

The average excretion of urinary dextrose of the period preceding the feeding of the Jerusalem artichoke was 6.26 Gm. and that of nitrogen 8.8 Gm. During the period when the Jerusalem artichoke was given the average amount of dextrose excreted daily in the urine was 8.47 Gm. and that of nitrogen 8.4 Gm. The reducing substance in the urine was here also proved to be dextrose. The average amount of dextrose excreted in the urine in the period following the feeding of oatmeal was 6.98 Gm. and that of nitrogen 9 Gm. The increase in the urinary dextrose while artichoke was given was 1.85 Gm.

In another experiment the amount of dextrose excreted in the urine before oatmeal was given was 6.98 Gm. and that of nitrogen 9 Gm. During the period in which oatmeal was given the urinary dextrose rose to 11.99 Gm. and the nitrogen to 8.9 Gm. In the period following, the urinary dextrose was 4.52 Gm. and the nitrogen 8.4 Gm. The increase in the urinary dextrose during the period in which oatmeal was given was 6.24 Gm.

COMMENT

Levulose, calculated from polariscopy, accounted for only 38 per cent of the total quantity calculated from the reduction of a hexose monosaccharide. In the experiment with the phlorhizinized dog the basal caloric and protein replacement was made with cream and casein, which kept the dog in good physical condition during a prolonged experiment of twenty-five eight hour periods. The extra dextrose obtained by feeding Jerusalem artichoke was 64.6 per cent of the theoretical available dextrose, a result comparable to that obtained when pure dextrose is fed.

In experiments 2 and 3 with diabetic subjects a method was developed for the study of the production and utilization of dextrose in food substances. In case 1 the increase in the amount of dextrose in the urine from ingested Jerusalem artichoke was greater than that from an equivalent quantity of oatmeal. In case 2 the increase in the urinary dextrose after ingestion of Jerusalem artichoke was less than that from an equivalent quantity of oatmeal.

CONCLUSION

From these experiments it is concluded that there is no striking difference in the utilization of Jerusalem artichoke in diabetes from that of an equivalent amount of oatmeal.

PHOSPHATASE STUDIES

III. SERUM PHOSPHATASE IN DISEASES OF THE BONE: INTERPRETATION AND SIGNIFICANCE

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The significance of phosphatase in the physiology of bone has been studied by Robison and his associates and reviewed by Robison [1] and Kay.[2] Kay [2a] and others [3] reported an increase of plasma phosphatase in several diseases of bone. We have also found increases of serum phosphatase when generalized osteoporosis was produced experimentally.[4]

Some of our other experimental results [5] indicate the untenability of the current view [1a] that an increase of plasma or serum phosphatase

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From the Laboratory Division, Hospital for Joint Diseases.

1. Robison, R.: (*a*) Bone Phosphatase, Ergebn. d. Enzymforsch. **1**:280, 1932; (*b*) The Significance of Phosphoric Esters in Metabolism (Three Herter Lectures), New York, New York University Press, 1932.

2. Kay, H. D.: (*a*) Plasma Phosphatase: II. The Enzyme in Disease, Particularly in Bone Disease, J. Biol. Chem. **89**:249 (Nov.) 1930; (*b*) Phosphatase in Growth and Disease of Bone, Physiol. Rev. **12**:384 (July) 1932.

3. (*a*) Roberts, W. M.: Variations in the Phosphatase Activity of the Blood in Disease, Brit. J. Exper. Path. **11**:90 (April) 1930. (*b*) Jenner, H. D., and Kay, H. D.: Plasma Phosphatase: III. A Clinical Method for the Determination of Plasma Phosphatase, Brit. J. Exper. Path. **13**:22 (Feb.) 1932. (*c*) Smith, J., and Maizels, M.: The Plasma Phosphatase in Rickets and Scurvy, Arch. Dis. Childhood **7**:149 (June) 1932. (*d*) Smith, J.: Plasma Phosphatase in Rickets and Other Disorders of Growth, ibid. **8**:215 (June) 1933. (*e*) Bennett, T. I.; Hunter, D., and Vaughan, J. M.: Idiopathic Steatorrhoea (Gee's Disease), Quart. J. Med. **1**:603 (Oct.) 1932. (*f*) Lister, W. A.: Idiopathic Steatorrhoea of Adults, Lancet **2**:15 (July 1) 1933.

4. Bodansky, A.; Jaffe, H. L., and Chandler, J. P.: (*a*) Serum Phosphatase Changes in Calcium Deficiency and in Ammonium Chloride Osteoporosis, Proc. Soc. Exper. Biol. & Med. **29**:871 (April) 1932; (*b*) Experimental Factors Influencing Blood Phosphatase Values, J. Biol. Chem. **97**:lxvi (July) 1932.

5. (*a*) Bodansky, A., and Jaffe, H. L.: Effects of Diet and Fasting on Plasma Phosphatase, Proc. Soc. Exper. Biol. & Med. **29**:199 (Nov.) 1931; (*b*) Phosphatase Studies: IV. Serum Phosphatase of Non-Osseous Origin; Significance of the Variations of Serum Phosphatase in Jaundice, ibid. **31**:107 (Oct.) 1933; (*c*) Bodansky, A.: Phosphatase Studies: VI. Non-Osseous Origins of Serum Phosphatase: Its Increase After Ingestion of Carbohydrates, J. Biol. Chem. **104**: 473 (March) 1934; (*d*) Bodansky, A.: Phosphatase Studies: VII. Inorganic Phosphorus and Phosphatase of the Serum in New Born Puppies, ibid. **104**:717 (March) 1934; (*e*) Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: VIII. Serum Phosphatase After Bile Duct Ligation in the Dog, Proc. Soc. Exper. Biol. & Med. **31**:1179 (June) 1934; (*f*) Bodansky, A.: Unpublished data.

is "confined almost exclusively to cases of bone disease." However, determinations of serum phosphatase still find their most useful application in the diagnosis of diseases of the bones. Variations of serum phosphatase which are not related to bone metabolism will be considered here only incidentally, and will be discussed elsewhere in greater detail.

Kay,[2a] Jenner and Kay [3b] and others reporting figures for plasma phosphatase in health and disease used Kay's [6] or Jenner and Kay's [3b] method of determination. The first of these methods yields low values, largely because of the retardation of hydrolysis of the substrate during the forty-eight hour period of incubation; the results obtained by the Jenner and Kay method are low because of the use of glycine to buffer the substrate. The ratios of the figures obtained by these investigators for plasma phosphatase in certain diseases of bone to those found for normal adults and children are also incorrect because the analytic errors are disproportionately greater when the plasma phosphatase content is high. These and some other errors have been avoided in our method for the determination of serum phosphatase.

SCOPE OF INVESTIGATION

We have determined the values for serum phosphatase (1) in normal children and adults and (2) in certain diseases of bone. These data have been used (3) to help establish serum phosphatase as an aid in diagnosis and in estimating the effectiveness of therapeutic measures. They may also be used as a basis for the consideration of the (4) biologic significance of variations in serum phosphatase in diseases of bone. Sufficient data are available in such a form as to realize these purposes. Some of the data must be published here in summary (for instance, those on rickets); they will be published later in full detail.

Our procedures for determining the inorganic serum phosphate and serum phosphatase have been described.[7] In the cases in which determinations of serum calcium seemed relevant we used a modified form of the Kramer-Tisdall method. Serum was obtained after fasting except as otherwise noted.

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6. Kay, H. D.: Plasma Phosphatase: I. Method of Determination, Some Properties of the Enzyme, J. Biol. Chem. **89**:235 (Nov.) 1930.

7. (*a*) Bodansky, A.; Hallman, L., and Bonoff, R.: Deviation from Beer's Law in the Kuttner-Cohen Method for Determination of Phosphorus, Proc. Soc. Exper. Biol. & Med. **28**:762 (April) 1931. Bodansky, A.: Phosphatase Studies: I. Determination of Inorganic Phosphate; Beer's Law and Interfering Substances in the Kuttner-Lichtenstein Method, J. Biol. Chem. **99**:197 (Dec.) 1932. (*b*) Bodansky, A.: Determination of Plasma Phosphatase, Proc. Soc. Exper. Biol. & Med. **28**:760 (April) 1931. (*c*) Bodansky, A.: Phosphatase Studies: II. Determination of Serum Phosphatase; Factors Influencing the Accuracy of the Determination, J. Biol. Chem. **101**:93 (June) 1933.

NORMAL VALUES FOR SERUM PHOSPHATASE [8]

Adults.—The serum of members of the laboratory and hospital staff and of several other normal adults, all apparently in good health, averaged 2.6 units of serum phosphatase per hundred cubic centimeters; 4 units was found in one case and about 1.5 in two; in the remaining twenty-one analyses the figures ranged between 2 and 3.5 units per hundred cubic centimeters, which is perhaps the more strictly normal

TABLE 1.—*Normal Values for Serum Phosphatase*

A. Adults

Case	Age	Sex	Per 100 Cc. of Serum: Phosphorus, Mg.	Phosphatase, Units	
1	16	M	3.6	1.6	T*
2	19	F	3.9	3.1	T
3	19	F	3.1	2.2	
4	20	F	4.0	2.4	
5	22	F	4.0	2.3	
6	25	F	3.6	2.1	
7	26	M	3.7	3.0	
8	26	M	3.7	4.0	
9	26	M	4.6‖	2.6	
10	26	M	3.5	3.2	
11	27	F	3.5	2.1	
12	27	M	3.8	2.5	
13	27	M	3.7	2.9	
14	27	M	3.4	2.2	
15	28	M	3.4	2.7	
16	29	M	3.8	3.3	
17	30	M	3.8	2.0	
18	30	M	3.7	1.5	
19	30	M	2.6	3.0	
20	32	M	3.4	2.6	
21	34	M	3.4	3.5	
22	34	F	2.9	2.2	
23	34	M	4.2	2.3	
24	44	M	3.0	2.4	
25¶	11	M	3.3	2.9	

B. Children

Case	Age	Sex	Per 100 Cc. of Serum: Calcium, Mg.	Phosphorus, Mg.	Phosphatase, Units	
1	2	F	....	5.8	7.2	T†
2	2	M	....	4.5	7.7	T
3	3	F	10.8	5.2	5.8	T‡
4	3	F	....	3.9	10.7	T‡
5	3	F	....	5.1	7.2	T†
6	3	F	....	4.9	7.8	T
7	4	F	....	4.7	5.3	T
8	4	M	....	4.3	5.2	P§
9	6	M	10.0	3.5	8.6	T‡
10	6	F	10.9	5.2	3.1	T‡
11	6	M	....	4.7	8.1	T
12	6	M	....	4.3	6.5	T‡
13	7	M	....	4.9	10.3	T
14	8	M	10.7	4.4	5.1	T‡
15	8	F	....	4.6	8.3	T†
16	9	M	10.7	4.3	8.1	T
17	9	M	....	4.0	7.6	P
18	9	M	....	3.7	8.0	P
19	9	M	....	4.2	8.4	P
20	10	F	....	5.8	6.0	T
21	10	F	....	4.5	8.5	T‡
22	11	M	10.2	5.3	10.0	T
23	12	F	10.2	4.9	8.9	T
24	12	F	....	3.6	11.4	P
25	13	M	10.9	4.3	5.3	T‡
26	14	M	10.6	5.1	13.1	T
27	15	F	....	4.0	5.5	P

* Tonsillectomy.
† Four hours after a light breakfast.
‡ Two hours after a light breakfast.
§ Poliomyelitis.
‖ The high serum inorganic phosphorus in this adult seems to have been due to daily ultraviolet irradiation for about five months.
¶ A case of sexual precocity, with pubic hair, etc., at 5.

range (table 1,A). An average of 3 units (maximum 3.9, minimum 1.6) was found in about a hundred miscellaneous hospital patients with a variety of clinical conditions, excluding only known diseases of bone and liver and jaundice, in which the value for serum phosphatase is higher than normal.

Children.—Young animals of every species which we have studied show higher values for serum phosphatase than adults of the same species.[5f] Table 1,B shows the values found in twenty-seven normal chil-

8. Brief summaries were presented at the annual meeting of the American Society of Biological Chemists, April, 1932,[4b] and were published recently.[7c]

dren. Twenty-one, admitted for tonsillectomy and in fair or good condition at the time, showed an average activity of serum phosphatase of 7.2 units per hundred cubic centimeters; in another group six children who had recovered from acute poliomyelitis and were in good health at the time of the test showed an average of 7.7 units per hundred cubic centimeters about six months after paralysis. The two groups are distinguished in table 1,B. The average for the twenty-seven children was 7.3; one low value of 3.1 units was found (child 10); the other values ranged between 5.1 and 13.1 units. The incidence of higher phosphatase values (from 10 to 13 units) was more frequent between the ages of about 10 and 15, and was perhaps related to the onset of puberty at varying chronological ages and to an increased rate of growth and metabolism.

Serum was obtained from about one half of the children after fasting; from the other half, two or four hours after a light breakfast; the averages in each group were similar.

In about three hundred children between 1 and 15 years of age hospitalized for a variety of clinical conditions (excluding anemia, malnutrition, jaundice and known disease of bone) the range of figures for serum phosphatase was approximately the same as in normal children (from 5 to 14 units). The average was about 7.5 units per hundred cubic centimeters. Higher values for infants up to a few months of age, from about 15 to 20 units per hundred cubic centimeters, were found in some hospitalized cases.

It may be noted that our average value for children is 2.7 times our average normal value for adults, while Kay's average for children is about 1.7 times his average value for adults.[2a]

The figures for the serum inorganic phosphate showed that in only four children (cases 4, 9, 18 and 24, table 1,B) were they lower than the typical values. Even if these cases were eliminated on the assumption that the serum inorganic phosphate indicated some deviation from the strictly normal state, the general average of serum phosphatase would be lowered only slightly, from 7.3 to 7 units.

The correlation between serum phosphatase and age in a group of normal children could have been demonstrated only by studying a much larger group than was feasible. We have, however, demonstrated this correlation in dogs examined repeatedly over a long period. We found a continuous decrease of serum phosphatase with an increase of age [5f] (after a sharp increase of serum phosphatase during the first forty-eight hours after birth,[5d] which is apparently due to the unique effect of nursing on the serum phosphatase of the new-born infant rather than to the specific effect of a particular foodstuff [5e]). It is obviously not feasible to conduct a study of individual children over a long period of time.

Our series of normal subjects and the larger number of hospitalized patients indicate that there is relatively little variation of serum phosphatase between 2 and 10 years of age. There is apparently a temporary rise between the ages of 10 and 15. At the age of 15 or 16, apparently depending on the anatomic stage of development, the serum phosphatase may be as low as 3 units per hundred cubic centimeters (even 1.6 units in case 1, table 1,A) and as high as 10 or 12 units, the latter values being plausibly associated at this age with active growth. The importance of physiologic age in determining the level of serum phosphatase is emphasized by a case of sexual precocity (case 25, listed with the cases of adults).

SERUM PHOSPHATASE IN DISEASES OF BONE

Local Atrophy of Bone.—A certain degree of atrophy of bone, a chronic atrophy of inactivity, is found in chronic arthritis and in other

TABLE 2.—*Serum Phosphatase in Generalized Osteoporosis*

Case	Sex	Age	Per 100 Cc. of Serum		
			Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units
1	F	50	10.0	3.3	6.6
Three weeks later	..	..	9.9	4.1	7.7
2	F	52	10.4	4.1	5.2
3	F	60	9.7	3.8	5.3
4	F	63	9.5	4.0	2.7*
5	F	68	9.1	2.8	2.2*
6	F	66	9.5	4.6	3.7

* Senile osteoporosis.

conditions involving a limited use of the extremities. In fourteen young and middle-aged adults with various chronic arthritides, serum phosphatase was at a high normal level, corresponding to slight atrophy of bone. In three cases the serum phosphatase was 5.1, 6.7 and 8.3 units per hundred cubic centimeters, respectively. In two of these pronounced local atrophy was found; we assume that it was present in the third, although the patient did not return for verification. It seems that a systematic study of arthritis from this standpoint (which is now in progress) is justified.

Generalized Osteoporosis.—Age is obviously a factor in determining the level of serum phosphatase in generalized osteoporosis. In the middle-aged the serum phosphatase may rise to about twice the normal average, while there is no rise in true senile osteoporosis. These results are in agreement with our observations in experimental osteoporosis. The experimental results also indicate that in young patients suffering from generalized osteoporosis a greater deviation from the normal can be expected. The figures for serum calcium and inorganic phosphorus were normal.

Hyperthyroidism.—In hyperthyroidism a negative calcium balance is sometimes to be expected. It is probable, however, that roentgenologic evidence of this will not always be present. In three patients with a high basal metabolic rate (from + 30 to + 70 per cent) the serum inorganic phosphorus and serum phosphatase were at the high normal level or higher. Only in one case (1, table 3) was there roentgenographic evidence of osteoporosis.

In a case still under observation, in which the initial basal metabolic rate was about +70 per cent, the serum phosphatase level rose over a period of about five weeks (the successive values being 5, 5.3, 6.2, 7.8 and 10.1 units per hundred cubic centimeters). The serum inorganic phosphorus figures during the same period remained fairly constant at 4.5 ± 0.3 mg. per hundred cubic centimeters.

Osteomalacia.—In osteomalacia a high level of serum phosphatase is associated with a low level of serum inorganic phosphorus, as in

TABLE 3.—*Serum Phosphatase in Hyperthyroidism*

			Per 100 Cc. of Serum			
Case	Sex	Age	Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units	Comment
1	F	41	10.5	4.6	4.8	Basal metabolic rate, +30 per cent; osteoporosis, spine and pelvis; sternum deformed
2	F	30	11.1	5.2	4.4	Basal metabolic rate, +70 per cent
3	F	46	10.2	3.7	4.0	Basal metabolic rate, +45 per cent

rickets. In a case of "nontropical sprue" (idiopathic steatorrhea) in a man about 40 years old we had similar results: serum calcium, 7.8 mg. per hundred cubic centimeters; serum inorganic phosphorus, 1.9 mg., and serum phosphatase, 8.2 units.

Hyperparathyroidism.—In one case of this relatively rare disease the serum phosphatase was 20.2 units; however, four months after the removal of a large parathyroid adenoma the phosphatase was 13.8 units per hundred cubic centimeters, and eight months after the operation, 12.1 units.[9] This case was complicated by renal dysfunction. Before operation the serum inorganic phosphorus was 7.1 mg. per hundred cubic centimeters, and was associated with 47.6 mg. of urea nitrogen per hundred cubic centimeters of blood, 10.1 mg. of uric acid and 5 mg. of creatinine, figures strikingly similar to those found in the disturbance of renal function in acute experimental hyperparathyroidism in dogs.

9. Our initial observations were made possible through the courtesy of Dr. A. Guttman and Dr. F. M. Hanger of the medical service of the Presbyterian Hospital, New York. We are indebted to Dr. William Barclay Parsons, Jr., of the surgical service of the Presbyterian Hospital, for the opportunity of making the postoperative observations.

The value for serum calcium, 13.1 mg. per hundred cubic centimeters, while only moderately high had undoubtedly been depressed by the high level of serum inorganic phosphate. The remarkable clinical improvement after the operation included also improvement in renal function, with a return to normal values for serum inorganic phosphorus; urea nitrogen was 29.3 mg. per hundred cubic centimeters of blood, uric acid

TABLE 4.—*Serum Phosphatase in Osteomalacia*

Case	Sex	Age	Per 100 Cc. of Serum		
			Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphotase, Units
1	F	20	....	1.6	10.3
2	F	40	9.5	1.5	11.1

TABLE 5.—*Serum Phosphatase in Paget's Disease (Osteitis Deformans)*

Case	Sex	Age	Per 100 Cc. of Serum			Degree of Involvement
			Calcium Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units	
				A. Polyostotic		
1	M	55	...	4.0	15*	
2	F	46	9.6	4.1	50	
3	M	68	...	2.9	52	
4	F	53	9.5	4.3	69	
5	M	48	9.8	3.5	70	
6	M	63	...	3.6	74	
7	F	53	...	3.7	76	
8	M	43	10.8	4.3	107	
9	M	55	...	4.0	114	
10	M	47	10.0	4.3	125	
				B. Localized		
11	F	69	10.0	3.5	4.9	Both tibias
12	M	66	9.5	2.5	5.9	
13	M	63	9.6	2.8	5.9	Ilium
14	M	70	...	3.6	6.6	Ilium, ischium, pubis
15†	F	62	9.2	5.0	10.2	Lower lumbar vertebrae, pelvis, hips
16	F	43	10.4	3.6	10.7	Both tibias
17	F	64	12.4	1.8	11.8	Skull, femur
18	M	56	10.9	3.6	12.0	Femur
19	M	50	10.2	3.4	15.4	Skull, tibia
20	F	52	10.2	3.4	17.2	
21	F	54	...	3.5	17.7	Pelvis, femur
22	F	50	...	3.2	17.9	Femur
23	F	56	9.9	3.8	23.1	Tibia, femur

* See text, page 95.
† Sister of patient in case 2.

6.4 mg. and creatinine 2.4 mg.; the serum calcium was at a low normal level, 8.9 mg. per hundred cubic centimeters.

Paget's Disease.—In florid polyostotic Paget's disease we have found from 50 to 125 units per hundred cubic centimeters (from 20 to 50 times the normal). In some cases of more or less localized Paget's disease the serum phosphatase was as low as 5 or 6 units per hundred cubic centimeters. Relatively lower values for phosphatase were found in the oldest subjects; in most cases this was undoubtedly due to localized

involvement, in others possibly to considerable spontaneous healing by sclerosis. The tendency to healing by sclerosis is observed in many advanced cases of Paget's disease: In one case (1, table 5,A) repeated analyses yielded consistent results, closely approximating the average figures of 4 mg. of inorganic phosphorus per hundred cubic centimeters of serum and 15 units of phosphatase. Postmortem examination confirmed the diagnosis of polyostotic Paget's disease, revealing involvement of the skull, pelvis, femurs, tibias, right humerus and left ulna, left shoulder girdle and chest.[10] Evidence of sclerosis was widespread, which explained the relatively low values for serum phosphatase.

It may be significant that the average age in the polyostotic group was 53 years, as compared with 58 years for the group with localized Paget's disease. Of eight patients over 60 years of age with Paget's disease only two suffered from the polyostotic form (serum phosphatase, respectively, 52 and 74 units) and six suffered from the more localized

TABLE 6.—*Age Incidence of Polyostotic and Localized Paget's Disease*

	Average Age	Total Number of Cases	Patients 60 Years and Older	
			Number of Cases	Percentage of Total
Polyostotic Paget's disease	53	10	2	20
Localized Paget's disease	58	13	6	47

involvement (17.7 units of serum phosphatase in one and from 4.9 to 11.8 in the remaining five).

It seems advisable to check in other cases, wherever found, the indicated correlation between age and the incidence of the polyostotic or the more localized forms of Paget's disease. Correlated determinations of serum phosphatase would be useful in this connection.

We may also point out the familial factor in Paget's disease in cases 2 and 15; one patient suffering from the polyostotic form and the other from localized involvement. It seems that the determination of serum phosphatase might offer a means of searching for the earliest evidence of Paget's disease within families in which the disease has been found in one or more of the members.

In a comparison of the analytic values found in hyperparathyroidism and Paget's disease it must be noted in the first place that the serum inorganic phosphorus is typically low in hyperparathyroidism and is frequently at a high normal level or just above it in Paget's disease. In one patient, however, a woman 64 years of age (case 17, table 5), the serum calcium was 12.4 mg. per hundred cubic centimeters, the serum inor-

10. Jaffe, H. L.: Paget's Disease of Bone, Arch. Path. **15**:83 (Jan.) 1933.

ganic phosphorus 1.8 mg. and the serum phosphatase 11.8 units. (Somewhat higher value for serum calcium and a lower value for inorganic phosphorus had been previously found in the same case in another laboratory.) The chemical findings indicated the possibility of hyperparathyroidism. The clinical diagnosis of Paget's disease was supported by the roentgen examination. This case was the only one of twenty-three observed by us in which the chemical changes usually associated with hyperparathyroidism were found in a case of Paget's disease. While in itself the association of these chemical and roentgenologic findings in the same case is interesting, the rarity of such association emphasizes the lack of basis for assuming hyperparathyroidism to be the etiologic factor in Paget's disease. It is well known that secondary enlargement of the parathyroid glands may be produced in experimental rickets and in experimental acidosis; the possibility of some secondary enlargement of the parathyroid glands in Paget's disease might therefore be conceded. However, pathologic hyperfunction is not necessarily associated with such secondary enlargement, and if parathyroid hyperfunction is sometimes associated with evidence of Paget's disease the association is rare indeed.[11]

A consideration of serum calcium, inorganic phosphorus and phosphatase in hyperparathyroidism and Paget's disease must be amplified

11. The belief held in some quarters that parathyroid function is of etiologic importance in Paget's disease is arrived at on the basis of reported observations of enlargement of the parathyroid glands in this condition and of alleged clinical improvement following removal of one or more such parathyroids (Ballin, M.: Ann. Surg. **96**:649, 1932; J. Bone & Joint Surg. **15**:120, 1933). Such supposedly enlarged parathyroids are considered to indicate hyperfunction and their removal is therefore considered justifiable by these observers. However, when critical judgment is applied to their reasons for calling these parathyroids hyperplastic, it soon becomes evident that there is no convincing basis for such assumption. To prove that a parathyroid of an adult is hyperplastic the gland must be fixed in a solution of formaldehyde, cut in frozen sections and stained with a fat stain. The presence of large numbers of principal cells containing little or no intracellular fat is at the present time the only valid microscopic evidence of such hyperplasia. The assumption of hyperplasia on the basis of increased size (unless this increase is very great) is unjustified, as it is established without doubt that in old and especially in senile persons the parathyroids may be somewhat enlarged even in the absence of osseous disease. Furthermore, the quantity of interstitial fat may be increased, and gross enlargement of the gland under such circumstances has no significance whatever. Pitted against this clinical and somewhat empiric view of the significance of the parathyroid in Paget's disease is the recent experience of patho-anatomists who have found that in most cases of Paget's disease the parathyroids are in no way abnormal, although they have also observed that mild degrees of secondary hyperplasia may occur. On theoretical grounds and on the basis of the present knowledge of the pathogenesis of Paget's disease any improvement that is alleged to follow the operation as such cannot be considered more than temporary, and it certainly does not establish parathyroid dysfunction as of etiologic importance in the disease.

by a statement of factors influencing these values and their interpretation. Nephritis, causing a rise of serum inorganic phosphate and a decline of serum calcium, may mask the evidence of these determinaions for true hyperparathyroidism. We think it advisable to determine urea or nonprotein nitrogen in all cases in which Paget's disease or hyperparathyroidism is suspected.

Reliance may be placed on the determination of serum phosphatase. The value of serum phosphatase as a criterion of disease of the bone is not impaired in the presence of nephritis. Serum phosphatase is, however, commonly increased in jaundice,[5b] so that determinations or estimates of the icteric index are desirable, particularly in those cases in which only a moderately high level of serum phosphatase is found. (We believe that the increases of serum phosphatase and of the icteric index represent disturbances of different functions of the liver, and

TABLE 7.—*Serum Phosphatase in Osteosclerosis Fragilis Generalisata*

Per 100 Cc. of Serum			
Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units	Comment
10.3	2.3	21.3	Initial analysis
10.3	2.3	21.4	Ten days later
			Wedge osteotomy seven days later
	2.8	16.7	Ten days later
	2.3	15.5	Forty-three days later

that increased values of serum phosphatase may be found in disturbances in the liver even in the absence of jaundice.[5c])

Osteosclerosis Fragilis Generalisata (*Albers-Schönberg Disease, Marble Bones*).—In one case of osteosclerosis fragilis generalisata in a youth 16 years of age, the activity of the serum phosphatase was from 2 to 3 times the average value for children and from about 5 to 8 times the average value for adults. We believe that in this case comparison with the adult is justified by the apparent physiologic age of the patient; the value for serum inorganic phosphorus supports this view.

(Osteotomy performed to correct deformities of bones is frequently followed by a decrease of serum phosphatase. This effect was found also after osteotomies performed for the correction of rachitic deformities, as well as in the case cited, and is apparently distinguished by its persistence from temporary postoperative decreases of serum phosphatase which we have observed following other operations. The decrease of serum phosphatase during the healing of an operative defect in abnormal bone seems significant. It suggests that the healing of the defect in some manner partially counteracts the disease process. However, other factors may be involved.)

Infantile Rickets.—The correlation of the activity of serum phosphatase with the pathologic process was strikingly indicated during the observation and treatment of a large number of children with rickets.[12]

In twenty-seven cases of active infantile rickets the serum phosphatase ranged from 30 to 190 units, about 4 to 25 times the normal average, depending on the severity of the condition. Negro children generally show the higher figures for serum phosphatase, associated with more severe clinical conditions. Previous irregular treatment with cod liver oil or exposure to the sun, particularly during the summer months, may be reflected in a milder clinical condition associated with only a moderately high level of serum phosphatase.

In active rickets, when no treatment was given, and on inadequate treatment, the serum phosphatase frequently continued to rise; when healing was slow on treatment with cod liver oil or small doses of viosterol, the phosphatase decreased slowly, if at all; on larger doses of viosterol, "minimum rapidly effective doses," there was a marked decrease of serum phosphatase within ten days or sooner; the continued rapid decrease of serum phosphatase was associated with other evidence of rapid healing. After treatment, for about two months, the phosphatase values remained constant, generally at a high normal level. The stabilized phosphatase value was reached in advance of the completion of the process of healing. Reconstruction of the bone may not be completed for months; when the reconstruction is complete, the serum phosphatase is within the normal range.

In some cases a diagnosis of rickets was based on the clinical signs (enlargement of the epiphyses, beading of the ribs, etc.). The serum phosphatase was within the normal limits, sometimes at a high normal level, suggesting that while the signs had persisted active rickets was no longer present. Roentgenologic examination confirmed the evidence of the determinations of serum phosphatase.

We shall publish elsewhere a more detailed study of phosphatase in rickets,[12] as the volume of our data does not permit their presentation and discussion at this time.[13]

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12. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: V. Serum Phosphatase as a Criterion of the Severity and Rate of Healing of Rickets, Am. J. Dis. Child., to be published.

13. After most of our work had been completed, Smith and Maizels[3c] and Smith[3d] published their studies of clinical rickets. The average plasma phosphatase in a series of seven normal children was 0.17 unit; in fourteen infants under 1 year, 0.23 unit, and in ten breast-fed infants from 6 to 8 months of age, about 0.25 unit. The maximum value reported in rickets was 1.4 units, or about 8 times the average normal figure in the series in which this value was reported. This was their highest ratio. The determinations were performed by a modification of Kay's method at p_H 7.6 and after incubation for forty-eight hours. We have criticized these conditions on theoretical as well as on practical grounds.[7c]

Fragilitas Ossium.—In two cases (2 and 3, table 8) the values for serum phosphatase were within the normal range. In case 3 the higher level of serum phosphatase possibly associated with this disease of the bones may have been lowered by anemia to the value actually found. In case 4, however, the level of serum phosphatase was definitely high. It seems that a study of special features that may be related to the different individual findings would be justified. In case 5, for instance, the high level of serum phosphatase was definitely related to late rickets (juvenile osteomalacia), which complicated this case. On treatment with viosterol the serum phospatase level declined (it may be noted that the serum inorganic phosphate remained low).

A familial factor was indicated by cases 1 and 2. The father had the typical blue sclera, although he had never sustained any fractures.

TABLE 8.—*Serum Phosphatase in Fragilitas Ossium*

			Per 100 Cc. of Serum			
			Calcium,	Inorganic Phosphorus,	Phosphatase,	
Case	Sex	Age	Mg.	Mg.	Units	Comment
1	M	38	10.2	2.8	2.4	Father of patient in case 2
2	M	3	....	4.0	7.0	Recent fracture
3	F	5	10.5	4.8	9.9	Recent fracture; anemia
4	F	5	11.2	4.8	19.1	Recent fracture
5	M	7	....	1.9	32.4	Late rickets also suggested
			9.8	1.8	35.2	3 years later; definite evidence of late rickets and diabetes insipidus
				1.5	28.7	10 days later; viosterol
				1.4	24.4	9 days later
			10.2	1.8	13.4	7 days later
			11.3	1.4	18.1	6 days later

Fractures.—A fracture may be related, in some cases at least, to a preexisting lesion of bone, for example, slight osteoporosis. For this reason it is impossible to conclude with certainty that the slight rise of serum phosphatase which was found in four of thirteen adults (cases 8, 15, 17 and 18, table 9) was due in every case to the fractures. On the other hand, it is suggestive that the four fractures had been sustained forty-two, four, eighteen and twenty-three days before the analyses, respectively, and at least three of them could be termed recent. In case 12, (a fracture 2 days old) the serum phosphatase was 3.5 units per hundred cubic centimeters (table 9).

In thirteen adults the average value was 3.9 units (minimum 2.1, maximum 8.5), which is distinctly higher than the normal average. In case 18 the levels of serum inorganic phosphorus and phosphatase were high twenty-three days after the fracture; three analyses done at intervals showed a regular decline within the next three weeks. The patient was not available for further examination.

A child (case 1) had a low value of 3.9 units per hundred cubic centimeters, associated with anemia; in four other children (cases 2 to 5) the values were substantially normal.

Osteomyelitis.—In patients with a destructive lesion like osteomyelitis, when it is moderate in extent and when there is little regeneration

TABLE 9.—*Serum Phosphatase After Fractures*

			Per 100 Cc. of Serum			
Case	Sex	Age	Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units	Clinical Notes
1	F	5	10.5	5.4	6.4	Right tibia, nonunion
2	F	6	10.3	4.3	3.9	Neck of humerus (15 days*); anemia
3	F	8	....	5.2	10.2	Right tibia, nonunion
4	M	11	....	6.0	6.4	Left humerus
				5.2	6.0	Ten days later
5	M	11	10.3	5.5	8.6	Left elbow (6 days)
6	M	21	10.3	4.9	2.4	Left mandible and humerus (56 days)
7	F	41	....	4.0	3.1	Surgical neck of left humerus
				5.0	3.4	Eleven days later
8	M	41	9.4	3.9	4.7	Left radius, ilium and wrist (42 days)
9	M	42	10.8	3.8	3.7	Right femur and patella, left tibia and fibula (60 days)
10	F	45	9.7	3.8	3.4	Left humerus, diabetes
11	M	47	....	2.8	2.3	Right humerus, nonunion
12	M	49	....	3.3	3.5	Skull, left humerus (2 days)
13	M	50	....	3.0	3.0	Nonunion
14	F	50	10.5	3.9	3.5	Neck of right femur, nonunion
				4.0	3.3	Sixteen days later
15	F	54	....	3.8	4.7	Upper third of right humerous (4 days)
16	M	60	10.0	3.2	2.1	Inner end of right clavicle
17	M	62	9.9	3.8	4.3	Right tibia (18 days)
18	F	65	....	5.3	8.5	Right humerus and radius (23 days)
				5.6	7.0	Five days later
				5.0	6.0	Ten days later
				4.5	5.7	Six days later

* The time elapsed after fracture was sustained has been noted in this and several other cases of "recent fractures."

TABLE 10.—*Serum Phosphatase in Osteomyelitis*

			Per 100 Cc. of Serum			
Case	Sex	Age	Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units	Comment
1	M	5	9.1	4.5	4.6*	Pulmonary tuberculosis; weight, 34 pounds (15.4 Kg.)
2	F	15	....	5.1	6.6	Right femur
3	F	10	....	4.9	8.4	
4	M	17	....	4.6	3.4	Right humerus
5	M	24	10.6	3.4	2.3	Ischium
6	M	43	10.1	3.3	4.8	Left humerus, radius and ulna

* The relatively low serum phosphatase in a child 5 years of age is adequately explained by the evident cachexia.

of bone, it seems that the serum phosphatase remains normal. It is possible that a moderate rise takes place when the lesion is more extensive (case 6, table 10). There seems to be some evidence that unusually high leukocyte counts may be associated with a slight increase of serum phosphatase. We think it desirable to bear this factor in mind in future studies of serum phosphatase in osteomyelitis.

Gaucher's Disease.—The serum phosphatase seems to be related to the degree of resorption of bone as well as to the anemic condition of the patient.

Cysts of Bone.—In one child (case 1, table 12) and four adults with localized cysts of the bones (as distinguished from generalized osteitis fibrosa cystica) the serum calcium, inorganic phosphorus and phosphatase were normal. The serum phosphatase was at a high normal level in cases 2 and 5 and distinctly above normal in case 4.

Tumors of Bone (Primary and Metastatic).—Metastatic carcinoma invading bone was associated with a definitely raised serum phosphatase.

TABLE 11.—*Serum Phosphatase in Gaucher's Disease*

			Per 100 Cc. of Serum		
Case	Sex	Age	Inorganic Phosphorus, Mg.	Phosphatase, Units	Comment
1	F	26	3.8	4.1	No changes in bone
		(9 weeks later)	3.9	3.5	
2	M	24	3.6	10.1	Resorption, pelvis and femurs
3	M	54	3.1	2.6	No changes in bone
4	F	30	4.7	2.3	No changes in bone
5	M	40	3.9	1.5	

TABLE 12.—*Serum Phosphatase in Cysts of Bone*

			Per 100 Cc. of Serum			
Case	Sex	Age	Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units	Comment
1	F	11	9.9	4.5	6.2	Left femur; anemia
2	F	..	....	4.5	4.1	Right humerus
			10.3	4.7	3.6	Five days later
3	M	23	....	3.9	3.3	Left humerus
4	F	46	10.6	3.8	6.0	
5	M	40	10.9	4.0	4.0	

The value for serum inorganic phosphorus was high; the serum calcium was normal (cases 1 and 2, table 13). A patient (case 3) with an undiagnosed metastatic tumor of the bone had a distinctly high level of serum phosphatase.

Osteogenic sarcoma (five cases) generally showed increased values; case 5 (sclerosing osteogenic sarcoma of the right humerus) showed a normal value. In two cases repeated observations were possible: In case 7 a diagnosis of sclerosing osteogenic sarcoma of the left tibia was made at a time when the phosphatase was 8.7 units per hundred cubic centimeters; two years later metastasis to the ribs had occurred and the phosphatase was 7 units. In case 8, under observation for a period of about five months, the phosphatase rose gradually.

In two of three cases of multiple myeloma a high value for serum calcium was found; this is a definite diagnostic sign, requiring differen-

tiation from hyperparathyroidism. In hyperparathyroidism, however, a low level of inorganic phosphorus is typical, while the value for serum phosphatase in one case observed by us was about 8 times the normal. The serum inorganic phosphorus was at the normal level in all three cases. In one case (11) the value for serum phosphatase was low;

TABLE 13.—*Serum Phosphatase of Patients with Tumors of the Bone*

			Per 100 Cc. of Serum			
Case	Sex	Age	Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units	Diagnosis
1	M	42	10.5	6.0	28.1	Carcinoma with metastases to bones
2	F	38	....	5.5	9.4	Carcinoma with metastases to lumbar vertebrae, sacrum, iliac bones and eleventh rib on left side*
3	F	40	9.6	3.3	12.0	Neoplasm of neck of right femur with metastases to skull (origin unconfirmed)
4	F	42	....	3.2	16.6	Osteogenic sarcoma of right femur, metastases to lungs
5	F	32	....	3.5	3.0	Sclerosing osteogenic sarcoma, right humerus
6	M	60	9.0	3.0	7.0	Osteogenic chondrosarcoma, right ilium
7	M	18	11.4	4.2	8.7	Sclerosing osteogenic sarcoma, left tibia
		20	10.6	4.0	7.0	Two years later; metastases to ribs
8	F	17	....	4.5	6.4	Osteogenic sarcoma
			10.6	4.0	5.6	Seventy-nine days later
				3.8	6.7	Forty-one days later
				3.8	7.1	Seven days later
				4.0	8.2	Thirteen days later
9	M	42	9.1	3.1	4.5	Recurring osteochondromas, left hip
10	M	..	....	3.1	4.8	Multiple myeloma
11	F	60	13.2	4.0	1.8	Multiple myeloma
12	M	40	16.1	3.4	4.9	Multiple myeloma
13	M	13	....	4.0	7.3	Medullary sarcoma (Ewing's tumor), spine and ribs; anemia
14	F	8	....	4.9	6.3	Medullary sarcoma (Ewing's tumor), left humerus; anemia
			11.2	5.4	4.6	Three months later
15	F	33	10.1	3.8	4.4	Giant cell tumor†
16	F	21	10.4	4.7	2.9	Giant cell tumor, right femur
17	M	16	10.2	4.7	3.3	Giant cell tumor removed ten weeks before; healing; anemia
			10.8	4.9	3.6	Twenty-six days later
18	M	50	9.3	3.0	4.3	Chordoma

* In a patient studied after this paper was completed (a woman 37 years of age) the initial serum phosphatase value was 56 units per hundred cubic centimeters; serum inorganic phosphorus, 4.9 mg., and serum calcium, 9.8 mg. Seven days later the serum phosphatase rose to 83 units, confirmed by a value of 85 units fifteen days later. There was no clinical evidence of Paget's or Recklinghausen's disease. A suspicion of multiple myeloma seemed to be ruled out by the serum calcium and phosphatase values. The chemical findings indicated a severe and progressive involvement of the bones; necropsy revealed an extensive sclerosing metastatic carcinoma involving practically all the bones of the skeleton. The primary lesion was in a bronchus and was not apparent clinically.

† See text, page 103.

in the two others it was about twice the normal average, and therefore lower than in hyperparathyroidism.

In two children with medullary sarcoma the serum phosphatase was normal; however, moderate anemia was present and no doubt masked the effect of the lesion of the bone.

In one case of giant cell tumor, and in another case after extirpation of a giant cell tumor, the serum phosphatase was normal (cases 16 and 17); in a third case presenting a giant cell tumor in one bone (diagnosis

confirmed) and an unidentified lesion in another bone (case 15) the serum phosphatase was slightly raised. Multiple giant cell tumors suggest hyperparathyroidism; however, the suspicion of Recklinghausen's disease was not supported in this case by other findings.

In chordoma (case 18) the serum phosphatase was slightly raised.

A better understanding of the significance of serum phosphatase in tumors of bone may be obtained after a comparison with the serum phosphatase in tumors without involvement of bone or liver, as a species

TABLE 14.—*Serum Phosphatase of Patients with Tumors Not Involving Bone*

			Per 100 Cc. of Serum		
Case	Sex	Age	Inorganic Phosphorus, Mg.	Phosphatase, Units	Diagnosis
1	F	45	3.7	2.7	Carcinoma of the thyroid
2	F	70	2.7	4.0	Carcinoma of the bladder; uremia; anemia
3	M	71	4.7	3.5	Adenocarcinoma of prostate gland
4	M	55	3.7	2.3	Large adenocarcinoma (?) in epigastric region
5	F	43	3.0	3.1	Metastatic tumor
6	M	47	2.8	2.3	Cystic adenoma of thyroid
7	F	30	4.2	3.2	Cystic adenoma of thyroid
8	F	41	3.3	3.0	Multiple fibromas of uterus and appendix
9	M	35	4.3	2.8	Liposarcoma; postoperative analysis
10	M	66	3.5	3.3	Myxochondrosarcoma
11	F	34	2.3	4.0	Undiagnosed
12	M	58	3.2	5.9	Large spindle cell sarcoma; anemia; icteric index, 5
13	F	50	2.5	6.9	Spindle cell fibrosarcoma, possible metastases to liver; icteric index, 61

TABLE 15.—*Serum Phosphatase in Calcinosis Universalis*

			Per 100 Cc. of Serum		
Case	Sex	Age	Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphotase, Units
1	F	29	9.2	3.8	3.1
Fourteen days later	..	..	...	3.9	3.1
2	F	30	...	3.4	3.0

of control (table 14). In these cases serum phosphatase seems to be substantially normal, from 2.7 to 4 units. In two cases of spindle cell sarcoma (cases 12 and 13, table 14) the serum phosphatase was 5.9 and 6.9 units per hundred cubic centimeters respectively. The icteric index in case 12 was, however, slightly higher than normal, while it was very high in case 13, in which there was suspicion of metastases to the liver.

Calcinosis Universalis.—Because of an assumed relation of this disease to calcium metabolism, the serum phosphatase was determined in two cases. Normal values were found.

Disturbances of Growth.—Serum phosphatase was only slightly raised in a case of acromegaly in a man, 50 years of age; the serum cal-

cium was 9.2 mg. per hundred cubic centimeters, the serum inorganic phosphorus 4 mg. and the serum phosphatase 4.9 units. In three cases of achondroplasia (two children and one adult) no clear shift of serum phosphatase from the normal was seen. The low normal phosphatase in the one adult is probably not related to achondroplasia; slight anemia was found, but its effect on the serum phosphatase cannot be affirmed with certainty in this case.

In one case of cretinism, in a girl about 4 years old, the initial serum inorganic phosphorus and phosphatase were 3.8 mg. and 5.3 units per hundred cubic centimeters, respectively. After twenty-one days of treatment with thyroid extract, the serum inorganic phosphorus was 5.3 mg. per hundred cubic centimeters and the serum phosphatase, 7.3 units. In a case of mongolism, in a girl about 2 months of age, 6.6 mg. of inorganic phosphorus and 7 units of phosphatase per hundred cubic centimeters of serum were found. In a case of amaurotic idiocy, in a boy

TABLE 16.—*Serum Phosphatase in Achondroplasia*

			Per 100 Cc. of Serum			
Case	Sex	Age	Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units	Comment
1	F	49	9.9	4.0	1.4	Slight anemia
2	M	9	10.4	4.7	8.0	Growth retarded at 13 months
3	F	7	10.8	5.1	6.3	Growth retarded at 3 years

2 years of age, 10.8 mg. of calcium, 5 mg. or inorganic phosphorus and 6.3 units of serum phosphatase per hundred cubic centimeters of serum were found.

CLINICAL INTERPRETATION OF VALUES FOR SERUM PHOSPHATASE

With the qualifications to be stated, our data may serve as an aid to a clinical interpretation of analyses of serum phosphatase. The values in polyostotic Paget's disease and rickets are characteristically high. In the latter, clinical improvement is unmistakably reflected in the decline of serum phosphatase; we believe that no suggested treatment of Paget's disease may be considered effective until the alleged improvement has been shown to be associated with a decrease of serum phosphatase. Osteoporosis (except senile osteoporosis), osteomalacia, hyperparathyroidism and certain malignant tumors of bone (primary or metastatic) are associated with definitely increased serum phosphatase. In various other diseases of bone the level of serum phosphatase, while not equally high, is significantly above the normal.

Other findings will necessarily affect the interpretation of serum phosphatase as an indication of involvement of bone. It is always necessary to consider such factors as senility, malnutrition and anemia, which lower the serum phosphatase, and jaundice and latent jaundice, as

well as involvement of the liver without jaundice, which may raise it. Chemical findings other than serum phosphatase (serum calcium, inorganic phosphorus, urea, nonprotein nitrogen, etc.) must also be considered. We need but mention the basic importance of clinical signs and symptoms, roentgen examinations, etc.

It must be noted particularly that moderately increased activity of serum phosphatase (from 4 to 14 units per hundred cubic centimeters in adults) is found also in catarrhal jaundice, in jaundice due to cinchophen poisoning and to arsphenamine intoxication, in cholecystitis with jaundice, in hepatitis, in tumors involving the liver and in some cases of anemia with a high icteric index.[5b] These conditions must be ruled out before one may infer from increased serum phosphatase that disease of bone is present. We have not found values of 5 units or higher in adults without evidence of involvement of bone or the liver. We are, indeed, inclined to regard any authentic value higher than 4 units as possibly abnormal.

In children, jaundice was associated with high, and anemia and cachexia with low values for serum phosphatase.

The effects of jaundice, anemia and cachexia on serum phosphatase were shown in the absence of disease of the bone.

SIGNIFICANCE OF VARIATIONS IN SERUM PHOSPHATASE

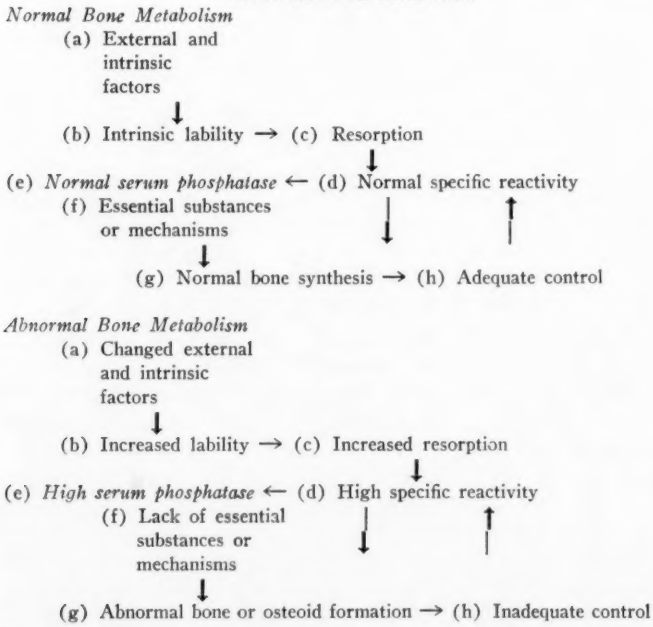
Robison showed that "the production of this enzyme [bone phosphatase] forms a part of cellular activities leading to the formation of bone."[1a] Kay explained the high plasma phosphatase in diseases of bone by leakage "at more than the normal rate, possibly because it is produced in excessive amount in the bones in attempted compensation for the lesion, or possibly because owing to weakness of the bones there is a greater amount of bending and crushing which mechanically squeezes out some of the cell contents."[2a]

These explanations fail, in their present formulation, to explain in a consistent manner the differences between serum phosphatase in various normal and pathologic states. The higher serum phosphatase of the young is indeed likely to be due to the greater "cellular activities leading to the formation of bone." However, this explanation does not cover the increase of serum phosphatase to the extremely high levels found in rickets or in Paget's disease; the difficulty is increased when the return to normal values after effective therapy is to be explained. The absence of an adequate explanation of the latter has been responsible for unjustified skepticism concerning not only the theories of the significance of serum phosphatase but also its value as an aid in diagnosis.

A formulation is required that would resolve these difficulties and that could be applied to variations in serum phosphatase in both normal and pathologic metabolism and in the course of effective therapy.

It may be suggested by way of an approach to such formulation, that variations in serum phosphatase, so far as they are related to bone metabolism, are an expression not of "cellular activities leading to the formation of bone," but rather of the "specific reactivity of bone," that is, its capacity for "cellular activities." This specific reactivity may be assumed to be a property of living bone at all times, even when normal cellular activities are rendered impossible for lack of suitable substances or because of the failure of necessary mechanisms. Furthermore, by analogy with the controls that maintain all metabolism at certain equilibriums, it is held that similar controls or inhibitions of the specific reactivity of bone are set up in the course of normal synthesis of bone; when normal synthesis does not occur, these controls are absent or inadequate, and specific reactivity is correspondingly higher; a high level of serum phosphatase is one expression of the high specific reactivity, and formation of normal bone (or osteoid) may be another. Inhibition of specific reactivity increases with age.[14]

The Manner in Which Serum Phosphatase Is Controlled in Normal and Abnormal Bone Metabolism


Normal Bone Metabolism
(a) External and intrinsic factors
(b) Intrinsic lability
(c) Resorption
(d) Normal specific reactivity
(e) Normal serum phosphatase
(f) Essential substances or mechanisms
(g) Normal bone synthesis
(h) Adequate control
Abnormal Bone Metabolism
(a) Changed external and intrinsic factors
(b) Increased lability
(c) Increased resorption
(d) High specific reactivity
(e) High serum phosphatase
(f) Lack of essential substances or mechanisms
(g) Abnormal bone or osteoid formation
(h) Inadequate control

14. Carrell, A., and Ebeling, A. H.: Age and Multiplication of Fibroblasts, J. Exper. Med. **34**:599 (Dec.) 1921.

The nature of the particular substance or mechanism that may be lacking for the normal synthesis of bone in a given disease of the bones is apparently of great importance. Deficiency of vitamin D (in clinical rickets) and the unknown etiologic factor of Paget's disease are apparently associated in severe cases with excessive syntheses of osteoid and of abnormal bone, respectively, and with very high values for serum phosphatase. On the other hand, in dietary calcium-phosphorus imbalance the moderately high phosphatase indicates specific reactivity to resorption of bone controlled at a moderately high level.

The decrease of serum phosphatase to normal after effective therapy in diseases of bones may be explained, somewhat schematically, as follows: substances or mechanisms necessary for normal synthesis of bone have been supplied; normal syntheses of bone consequently take place; these lead in turn to the appearance of inhibitions of specific reactivity; specific reactivity controlled at the successively lower levels is expressed by successively lower phosphatase values; when normal specific reactivity is reached, it is expressed by normal serum phosphatase.

COMMENTS

Our view of serum phosphatase as an expression of the "controlled specific reactivity" of bone may be verified by relating the known facts of bone metabolism in health and disease to the corresponding values for serum phosphatase.

In the normal young animal, bone is normally more labile, more susceptible to resorption, than in the adult. The production of experimental rickets in young animals is facilitated by this greater lability. The successful use of young animals in producing experimental hyperparathyroidism was based on the same principle;[15] it is also significant that

15. Bodansky, A.; Blair, J. E., and Jaffe, H. L.: Serum Calcium and Phosphorus of Guinea-Pigs After Administration of Single and Repeated Doses of Parathormone, Proc. Soc. Exper. Biol. & Med. **27**:708 (April (1930); Experimental Hyperparathyroidism in Guinea-Pigs Leading to Ostitis Fibrosa, J. Biol. Chem. **88**:629 (Oct.) 1930. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: Production in Guinea-Pigs of Fibrous Bone Lesions with Parathyroid Extract, Proc. Soc. Exper. Biol. & Med. **27**:710 (April) 1930; Influence of Age on the Effect of Parathormone on Guinea-Pig Bones, ibid. **28**:174 (Nov.) 1930; Fibrous Osteodystrophy (Osteitis Fibrosa) in Experimental Hyperparathyroidism of Guinea-Pigs, Arch. Path. **11**:207 (Feb.) 1931; The Influence of Age and of Duration of Treatment on the Production and Repair of Bone Lesions in Experimental Hyperparathyroidism, J. Exper. Med. **55**:139 (Jan.) 1932. Jaffe, H. L., and Bodansky, A.: Experimental Ostitis Fibrosa Cystica in Dogs, Proc. Soc. Exper. Biol. & Med. **27**:795 (May) 1930; Experimental Fibrous Osteodystrophy (Ostitis Fibrosa) in Hyperparathyroid Dogs, J. Exper. Med. **52**:669 (Nov.) 1930. Bodansky, A., and Jaffe, H. L.: Experimental Chronic Hyperparathyroidism in Dogs Without Hypercalcemia, Proc. Soc. Exper. Biol. & Med. **27**:797 (May) 1930; Parathormone Dosage and Serum Calcium and Phosphorus in Experimental Chronic Hyperparathyroidism Leading to Ostitis Fibrosa, J. Exper. Med. **53**:591 (May) 1931.

the zones of most active growth were most actively resorbed.[16] Young animals are also more susceptible to the effects of a dietary deficiency in calcium and experimental acidosis.[17] However, the greater specific reactivity of the normal young to resorption of bone is controlled at its relatively high level, remaining within certain limits, leading to a higher serum phosphatase on one hand and to growth of bone on the other.

In normal adults lower specific reactivity (to slower resorption) involves both slower normal formation of bone and a relatively lower level of serum phosphatase than in children, whereas in senility slow resorption occurs, but specific reactivity is relatively slight;[14] both synthesis of bone and serum phosphatase are at their lowest.

In osteoporosis specific reactivity is stimulated in accordance with the degree of resorption; however, as is obvious, synthesis of bone is inadequate because of the lack of an essential substance or mechanism; adequate controls are therefore not set up; and serum phosphatase increases—most in the young, moderately in the middle-aged and slightly or not at all in the senile.

In hyperparathyroidism the generalized resorption of bone stimulates specific reactivity. However, the virtual calcium-phosphorus imbalance of the hyperfunction permits only relatively slight bone or osteoid synthesis. The controls are therefore inadequate, and serum phosphatase rises. The resorption in hyperparathyroidism being more active than in generalized osteoporosis, specific reactivity and serum phosphatase are controlled at a higher level.

In Paget's disease the typical mosaic structure of the newly formed bone indicates rapid transformation of bone.[10] The inorganic serum phosphate in the florid cases is frequently near the upper limit of normal; widespread resorption stimulates cellular activity, but, as has been stated, the newly formed abnormal bone cannot set up adequate controls of specific reactivity; the rapid rate of abnormal formation of bone and extremely high serum phosphatase correspond to the thus inadequately controlled specific reactivity (outline). Senility seems to be a factor in Paget's disease, the oldest patients showing the lowest values for serum phosphatase, in part probably owing to localized

16. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: Rate of Decalcification and the Sites of Bone Lesions in Experimental Hyperparathyroidism, Proc. Soc. Exper. Biol. & Med. **28**:793 (Jan.) 1931; The Sites of Decalcification and of Bone Lesions in Experimental Hyperparathyroidism, Arch. Path. **12**:715 (Nov.) 1931.

17. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: The Effects of Parathormone and Ammonium Chloride on the Bones of Rabbits, J. Exper. Med. **55**:695 (May) 1932. Jaffe, H. L.; Bodansky, A., and Chandler, J. P.: Ammonium Chloride Decalcification, as Modified by Calcium Intake: The Relation Between Generalized Osteoporosis and Ostitis Fibrosa, ibid. **56**:832 (Dec.) 1932; footnote 4.

involvement and spontaneous healing by sclerosis,[10] but in part, possibly, because of the lower specific reactivity of the old.

In active rickets normal synthesis of bone does not take place; adequate controls of specific reactivity are therefore not set up; excessive formation of osteoid and high values for serum phosphatase are expressions of specific reactivity controlled at a very high level. Effective therapy results in normal synthesis of bone, so that more adequate controls appear and the decrease of serum phosphatase expresses the specific reactivity controlled at successively lower levels. During reconstruction of the bone the serum phosphatase may remain at a high normal level, but when reconstruction is complete the serum phosphatase is within the normal range.

Osteomyelitis causes no marked rise of serum phosphatase. In the case of such destructive lesions, the principle that applies could probably be expressed as follows: Necrotic bone is not capable of reactions leading to an increased serum phosphatase. New formation of bone, when it occurs, may cause a rise of serum phosphatase. Leukocytosis *per se* may cause a slight rise of serum phosphatase, which is of course not related directly to metabolism of bone.

In experimental acidosis and deficiency in calcium the negative balance is due to a relative increase of resorption and a decrease of normal synthesis of bone; the former stimulates and the latter fails to control specific reactivity adequately. Specific reactivity and serum phosphatase are therefore controlled at a higher level.

SUMMARY

1. Serum phosphate is of diverse origin (from bone, the liver, etc.). The normal range of serum phosphatase in adults is between 1.5 and 4 units per hundred cubic centimeters (average about 2.5) and in children between 5 and 14 (average about 7). Higher values are found clinically in involvements of the bone and liver; lower values, in anemia and cachexia. When serum phosphatase is to be used as an aid in clinical diagnosis of diseases of the bone it has been shown that involvement of the liver with or without jaundice must be ruled out; and when serum calcium and determinations of inorganic phosphate are also to be considered, renal involvement must be eliminated.

2. Destruction of bone *per se,* unless accompanied by new bone or osteoid formation, is probably not associated with a marked rise of serum phosphatase.

3. In diseases of bone serum phosphatase is highest when it is associated with excessive formation of abnormal bone (polyostotic Paget's disease) and with excessive formation of osteoid (rickets). Successful therapy in rickets and hyperparathyroidism resulted in a lowering of the

level of serum phosphatase. In Paget's disease spontaneous healing by sclerosis was associated with relatively low values for serum phosphatase. Localized Paget's disease (and a moderately high level of serum phosphatase) was relatively more frequent in patients over 60 years of age.

4. The use of determinations of serum phosphatase as a criterion of effective therapy in rickets and healed rickets, and in the differential diagnosis of Paget's disease, Recklinghausen's disease, multiple myeloma and tumors of the bone has been discussed.

5. Variations in serum phosphatase, so far as they may be related to bone metabolism, are assumed to be an expression of "controlled specific reactivity" to resorption of bone (normal and pathologic). The mechanism by which the specific reactivity of bone and the level of serum phosphatase are controlled at normal or high levels has been suggested.

6. Clinical and experimental studies are suggested in connection with the changes in the bones in arthritis, fragilitas ossium, fractures and similar conditions.

FURTHER OBSERVATIONS ON THE EFFECT OF DRUGS ON INDUCED CARDIAC STANDSTILL

EFFECT OF EPINEPHRINE AND RELATED COMPOUNDS

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The heart possesses several important properties. The function most familiar to the clinician is contractility which, when impaired, leads to the frequently observed slow cardiac failure. Sudden cessation of the cardiac activity, however, results from disturbance in another essential property of the heart, that of stimulus formation, termed rhythmicity or automaticity. Normally the sinus node produces the stimulus necessary for cardiac contraction, and the activity of the heart abruptly ceases if this or other rhythmic centers fail to function. Absence of an impulse-initiating mechanism is the cause of the ventricular standstill in complete heart block. The frequency with which impairment of the rhythmic function occurs in other clinical conditions is uncertain, but it probably plays a part in the sudden cardiac arrest occasionally observed on the operating table. The success with which intracardiac injection has resuscitated the asystolic heart in shock, asphyxia and various types of poisoning indicates that the abnormal physiologic mechanism may be present in a variety of clinical conditions.

Previous studies concerned with the effect of drugs on the impulse-initiating property of the heart consist of observations in the experimental animal in which total cardiac standstill has been produced by elimination of the normal pacemaker, or ventricular standstill by the induction of heart block. Clinical studies consist of reports on the response of the asystolic heart to various types of intracardiac injections and on the effect of drugs in the prevention of Adams-Stokes seizures of heart block. These methods have not resulted in a general agreement as to the efficiency of drugs in the prevention and treatment of cardiac standstill.

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In 1866 Czermack [1] demonstrated that digital pressure on the neck in the region of the vagus nerve causes a slowing of the cardiac activity. The observations of Hering [2] indicated conclusively that this phenomenon is not due to a direct stimulation of the vagus nerve but is the result of a reflex which originates in a specialized portion of the internal carotid artery, the carotid sinus. In many persons, apparently owing to an overactivity of the vagus nerve,[3] prolonged cardiac standstill may be induced. Electrocardiographic observations indicate that the standstill is due to a temporary inactivity of the sinus node and to failure in the formation of secondary centers of impulse initiation. In previous reports [4] it was pointed out that these subjects permit a direct and well controlled method for the study of the effect of drugs on the

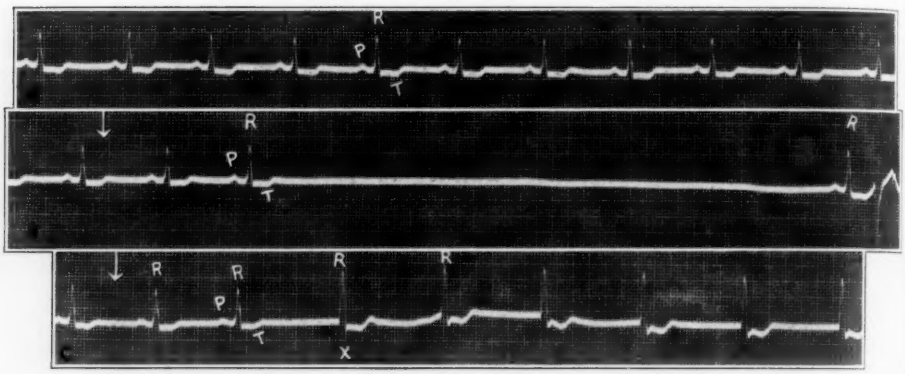

Fig. 1 (H. B.).—*A*, lead II before pressure on the carotid sinus. *B*, the effect of pressure on the right carotid sinus is indicated by the arrow. There is a cardiac standstill of seven and one-half seconds; *C*, compression of the right carotid sinus after administration of 1 cc. of epinephrine (1:1,000). Note the alteration in the ventricular complexes and the absence of the P wave starting at *X*, indicating the development of a ventricular rhythm.

impulse-initiating property of the heart. The evidence that a drug increases cardiac rhythmicity is the prevention of cardiac standstill by

1. Czermack, J. N.: Ueber mechanische Vagusreizung beim Menschen, Jenaische Ztschr. f. Med. u. Naturw. **2**:384, 1866.

2. Hering, H. E.: Die Karotissinus-Reflexe auf Herz und Gefässe, Dresden, Theodor Steinkopff, 1927.

3. Nathanson, M. H.: Site of Hypersensitiveness of the Exaggerated Sinus Caroticus Reflex, Proc. Soc. Exper. Biol. & Med. **29**:1037, 1932.

4. Nathanson, M. H.: A Method for the Study of the Rhythmic Property of the Human Heart, Proc. Soc. Exper. Biol. & Med. **30**:967, 1933; Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, Arch. Int. Med. **51**:387 (March) 1933.

the formation of a new impulse-initiating center during the period of inactivity of the sinus node.

Observations on the effect of drugs on this type of standstill were carried out on a number of suitable subjects, most extensively on one patient (H. B.) who was especially favorable for this type of study. He was an elderly man in whom an exaggerated response to pressure on the carotid sinus could be obtained with remarkable ease and with only slight discomfort. Moderate compression of the carotid sinus elicited a standstill varying from seven to nine seconds (fig. 1 *B*) which could be repeated with great consistency over a long period of time. In numerous control records there was no indication of a contraction from an ectopic focus during the period of stimulation of the sinus carotid. Similar control studies were carried out on other subjects. Each experiment consisted of a control electrocardiogram recording the effect of pressure on the right carotid sinus. The drug was then administered, and records were taken after suitable intervals, again observing the effect of stimulation of the carotid sinus. The present report consists of the results obtained by this method with (1) a group of drugs selected because they have been suggested in the treatment or prevention of cardiac standstill, and (2) a group of substances which are related in chemical structure to epinephrine. The first group includes epinephrine, ephedrine, barium chloride, calcium gluconate, digitalis, caffein, coramin, metrazol and thyroxine.

DRUGS SUGGESTED IN THE TREATMENT OR PREVENTION OF CARDIAC STANDSTILL

Epinephrine.—Rothberger and Winterberg [5] demonstrated that in the experimental animal stimulation of the left sympathetic nerve or the administration of epinephrine prevents the cardiac standstill produced by stimulation of the vagus nerve. Cullis and Tribe [6] showed that this drug increases both the auricular and the ventricular rate in experimental heart block. Since 1916 epinephrine has been used in heart block, usually with favorable results, although apparent ineffectiveness has also been reported. Epinephrine was studied in eight subjects by the present method, and in every case 1 mg. of epinephrine administered subcutaneously abolished the cardiac standstill by the initiation of a ventricular rhythm (fig. 1).

Ephedrine.—Several observers have reported favorable results in the prevention of Adams-Stokes seizures of heart block by the oral

5. Rothberger, C. J., and Winterberg, H.: Ueber die experimentelle Erzeugung extrasystolischer ventrikulärer Tachykardie durch Accelleransreizung, Arch. f. d. ges. Physiol. **142**:461, 1911.

6. Cullis, W. E., and Tribe, E. M.: Distribution of Nerves in the Heart, J. Physiol. **46**:141, 1913.

administration of ephedrine.[7] Cheer, Tung and Bien,[8] however, reported no increase in ventricular rate in a case of complete heart block after the administration of 150 mg. of ephedrine by mouth. In H. B. large doses of this drug administered orally and subcutaneously were without effect on the cardiac arrest. In another subject 30 mg. of ephedrine was ineffective by intravenous injection, but thirty minutes later 0.1 mg. of epinephrine abolished the standstill. This suggested some qualitative difference in the action of the two related substances, but later studies indicated that the differences were entirely quantitative and that an insufficient dosage of ephedrine had been used. In H. B. 50 mg. of ephedrine given intravenously was without effect, but when

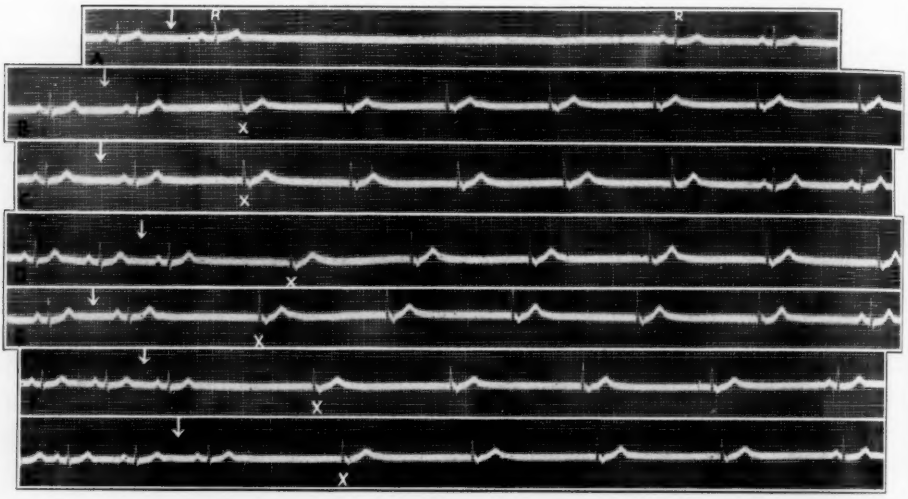

Fig. 2 (J. C.).—*A* shows a cardiac standstill of six and two-tenths seconds on pressure on the right carotid sinus, indicated by the arrow. *B*, a tracing made after the intravenous injection of 50 mg. of ephedrine sulphate, shows a ventricular rhythm starting at *X* with pressure on the carotid sinus. *C*, taken one hour after the injection, still shows an active effect.

the dose was increased to 100 mg. a reaction similar to that produced by epinephrine was obtained. More recently two other subjects were

7. Miller, T. G.: A Consideration of the Clinical Value of Ephedrine, Am. J. M. Sc. **170**:157, 1925. Fahr, George: personal communication to the author. Hollingsworth, M.: Ephedrine in Adams-Stokes Syndrome, California & West. Med. **26**:802, 1927. Stecher, R. M.: A Note on Adams-Stokes Disease Treated with Ephedrine, Am. Heart J. **3**:567, 1928. Wood, J. E., Jr.: Ephedrine in Adams-Stokes Syndrome, J. A. M. A. **98**:1364 (April 16) 1932.

8. Cheer, S. N.; Tung, C. L., and Bien, C. W.: Combined Effect of Ephedrine and Atropine on Complete Heart Block, Am. Heart J. **8**:400, 1933.

available, and in both 50 mg. of ephedrine by intravenous injection was effective (fig. 2). In three subjects it was possible to compare the reactions of epinephrine and ephedrine; this will be reserved for a later portion of this report.

Barium Chloride and Calcium Gluconate.—The work of Rothberger and Winterberg [5] indicates that salts of barium and calcium increase the rhythmicity of the ventricles and that with large doses various types of ventricular rhythm occur to the point of ventricular fibrillation. These experiments formed the basis for the use of barium chloride in clinical heart block.[9] The drug has been used with apparent benefit in the prevention of the Adams-Stokes seizures, but unfavorable reports also appear in the literature.[10] Barium chloride was used in two cases in doses of from 200 to 250 mg. a day by mouth. In one patient the drug had no effect on the induced cardiac standstill. In another subject, J. M., the cardiac arrest was prevented by the development of an idioventricular rhythm. Large oral and intravenous doses of calcium gluconate had no effect.

Digitalis.—It is well known that digitalis administered in large doses increases the irritability of the ventricles as evidenced by the occasional development of ventricular extrasystoles and tachycardias. It was repeatedly demonstrated in H. B. that daily doses of 0.2 Gm. of digitalis definitely increased the duration of the standstill up to fifteen or sixteen seconds. When administered in these doses the drug did not increase the irritability of the ventricles sufficiently to bring about development of an ectopic rhythm. The prolongation of the standstill may be explained by the increased sensitivity of the vagus nerve which is one of the effects of digitalis. The absence of an idioventricular rhythm agrees with the observations of Schwartz [11] who showed that augmentation of the automatic ventricular rate in complete heart block occurs only with toxic doses of digitalis.

Caffeine.—Von Egmond [12] observed a transient increase in the ventricular rate in experimental heart block after the administration of caffeine. However, the effect occurred only with amounts far above the usual therapeutic dose. Hirschfelder [13] stated that caffeine has no

9. Cohn, A. E., and Levine, S. A.: The Beneficial Effects of Barium Chloride on Adams-Stokes Disease, Arch. Int. Med. **36**:1 (July) 1925.

10. Parsonnet, A. E., and Hyman, A. S.: Barium Chloride in Stokes-Adams Syndrome of Complete Heart Block, Am. J. M. Sc. **180**:356, 1930.

11. Schwartz, S. P.: The Action of Digitalis on Complete Heart Block, Am. Heart J. **4**:408, 1929.

12. von Egmond, A. A. J.: Ueber die Wirkung einiger Arzneimittel beim volständigen Herzblock, Arch. f. d. ges. Physiol. **154**:39, 1913.

13. Hirschfelder, A. D.: Diseases of the Heart and Aorta, ed. 3, Philadelphia, J. B. Lippincott Company, 1918, p. 587.

effect on the ventricular standstill of clinical heart block. In H. B., 0.7 Gm. of caffeine sodium benzoate was injected intravenously and did not influence the cardiac standstill.

Coramin and Metrazol.—These substances have actions similar to those of camphor and have been recommended as acute circulatory and respiratory stimulants. Both substances have been used with apparent success in resuscitation by intracardiac injection into the asystolic heart. As was pointed out by Hyman,[14] it is difficult to determine whether it is the drug or the needle puncture which restores the rhythmic function to the heart. In H. B., 3 cc. of coramin injected intravenously, and on another occasion 2 cc. of metrazol, was without effect on the induced cardiac standstill.

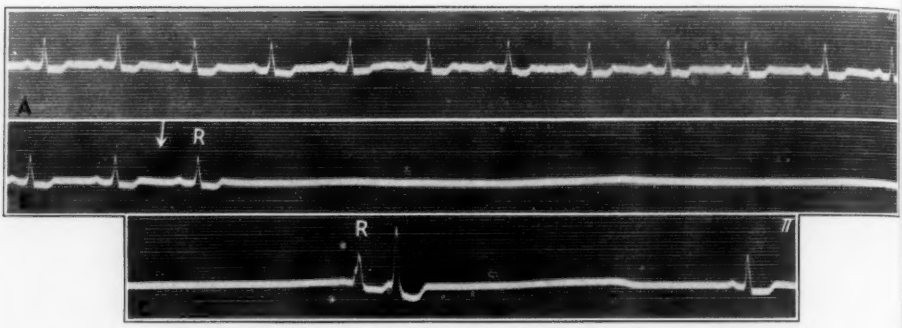

Fig. 3 (H. B.).—*B* and *C* show a standstill of ten and eight-tenths seconds. At this time the patient had received 15 mg. of thyroxine intravenously in divided doses.

Thyroxine.—That thyroxine increases the irritability of the heart is suggested by the tachycardia of hyperthyroidism. It has been demonstrated that thyroxine acts directly on the heart.[15] It increases the pulsation of cardiac muscle preparations which are devoid of nerve tissue. Thyroxine and thyroid have been used with variable results in clinical heart block. Blackford and Willius[16] and Drake[17] reported

14. Hyman, A. S.: Resuscitation of the Stopped Heart by Intracardiac Therapy, Arch. Int. Med. **46**:553 (Oct.) 1930.

15. Markowitz, C., and Yater, W. M.: Response of Explanted Cardiac Muscle to Thyroxine, Am. J. Physiol. **100**:162, 1932.

16. Blackford, J. M., and Willius, F. A.: Chronic Heart Block, Am. J. M. Sc. **154**:585, 1917.

17. Drake, E. H.: A Case of Complete Heart Block with Interesting Reaction to Drugs, Am. Heart J. **3**:560, 1928.

clinical improvement, while Aub and Stern [18] found that large doses of thyroid increased the auricular rate but did not influence the ventricular rate. In H. B., 15 mg. of crystalline thyroxine was administered intravenously in divided doses over a period of five days. The basal metabolism increased from zero to plus 22. Pressure on the right carotid sinus repeatedly induced a long cardiac standstill (fig. 3).

EPINEPHRINE AND CHEMICALLY RELATED COMPOUNDS

The powerful and consistent action of epinephrine and, to a lesser degree, of ephedrine suggested that the prevention of cardiac standstill may depend on the stimulation of the accelerator nervous mechanism of the heart. It seemed, therefore, of importance to study the effect of other drugs which have a similar type of action. Shortly after the discovery of the chemical structure of epinephrine, the physiologic activity of a number of related compounds was investigated. In 1910 Barger and Dale [19] carried out extensive studies and found that sympathetic stimulation which they termed sympathomimetic action was produced by many epinephrine-like substances and that the intensity of the effect increased as these substances approached the composition of epinephrine itself. In all the investigations the response of the blood pressure in the experimental animal has been used almost exclusively as the index of the comparative activities of these epinephrine-like compounds. The quantitative value of the different groups in the epinephrine molecule has been estimated by this method, and this has formed the basis for the synthesis of additional compounds. It was pointed out by Barger and Dale [19] that a substance showing an epinephrine-like pressor response may not reproduce all the other effects of epinephrine in the same degree. Since there do not appear to be any reports on the relative effects of these compounds on the human heart, a study was carried out by the present method to determine the influence of chemical structure on this particular physiologic action. Aside from theoretical considerations, this seemed to be of some practical importance, since a number of synthetic substances are now marketed as substitutes for epinephrine.

The reaction to natural epinephrine was used as a standard for comparison, and the response to varying doses of epinephrine was first

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18. Aub, J. C., and Stern, N. S.: The Influence of Thyroid Extract on the Total Metabolism and Heart in a Case of Heart Block, Arch. Int. Med. **21**:130 (Jan.) 1918.

19. Barger, G., and Dale, H. H.: Chemical Structure and Sympathiomimetic Action of Amines, J. Physiol. **41**:19, 1910.

determined. After a control electrocardiogram showing the effect of pressure on the carotid sinus had been made, the drug was administered intravenously, and records were taken after one minute, and then at frequent intervals thereafter until the standstill could again be reproduced. The reactions to 0.2, 0.05, 0.02 and 0.01 mg. were obtained in this manner. The results were a series of electrocardiograms in which the rate of the ectopic pacemaker and the duration of the effect could be determined. Repeated injections of these doses at different times revealed a definite consistency in the reactions. It was found that the rate of the ectopic pacemaker and the duration of the effect were proportional to the dose

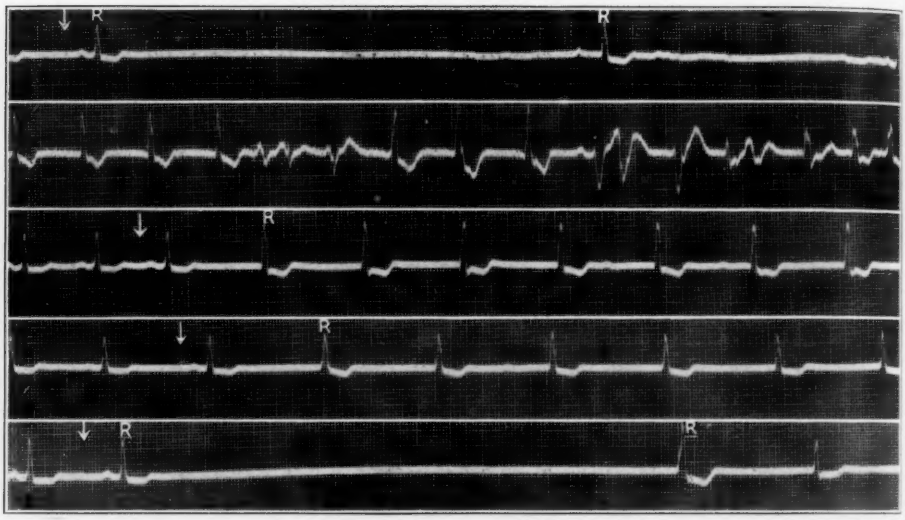


Fig. 4 (H. B.).—*A* shows an induced standstill of six seconds. *B* shows a maximum rate of 100 with multiple rhythmic foci. *C* and *D* were made after the intravenous administration of 0.2 mg. of l-epinephrine. *E* was made twenty-five minutes after the injection.

administered. For example, 0.2 mg. of epinephrine resulted in a rapid ventricular rhythm from multiple foci, the maximum rate being 100 and the duration twenty-five minutes (fig. 4). The smaller doses induced ventricular rhythms from a single focus, the rate and duration varying with the dose (figs. 5 and 6). The reactions of the epinephrine-like compounds were studied in the same manner, and the resulting records compared with those obtained with the different doses of epinephrine, thus permitting an estimation of the ratio of activity between epinephrine and the related compounds.

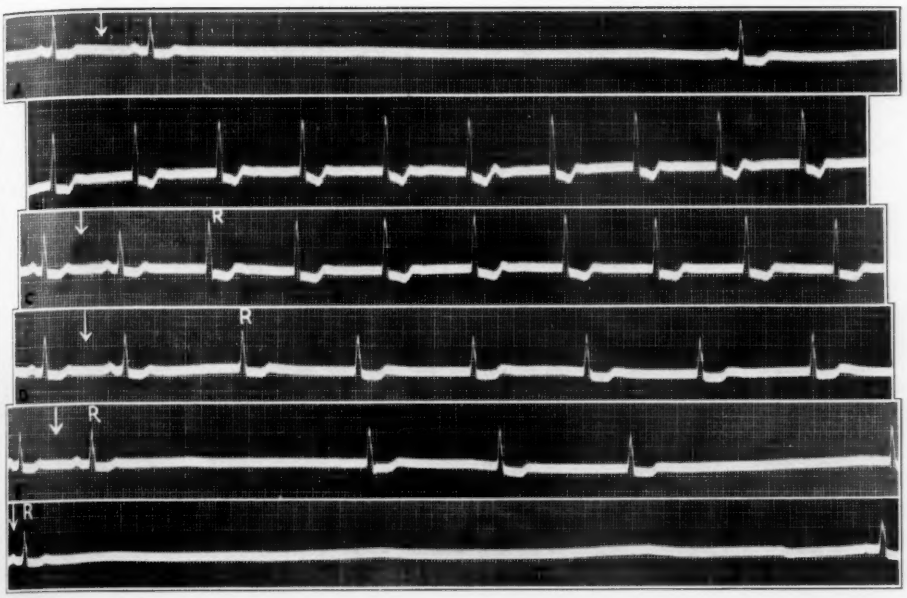


Fig. 5 (H. B.).—*A* shows an induced standstill of seven and six-tenths seconds. *B*, taken one minute after the intravenous administration of 0.05 mg. of l-epinephrine, shows ventricular rhythm; the rate is 60. *E* shows the disappearance of the effect fifteen minutes after the injection of the drug.

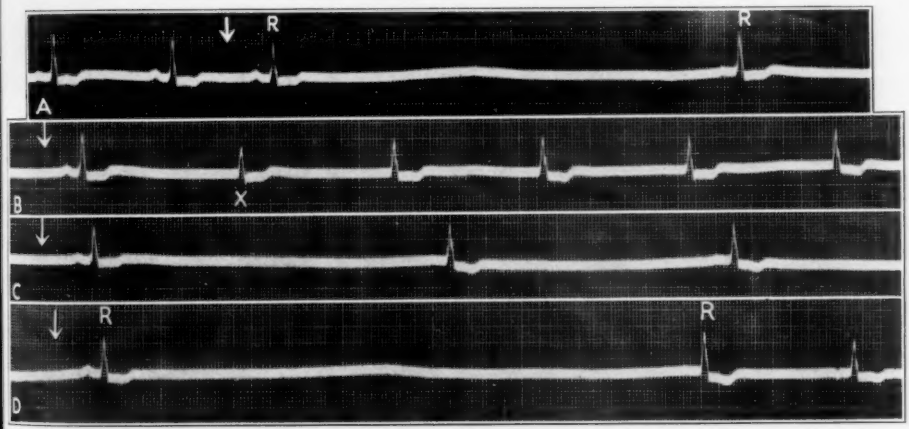
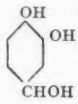


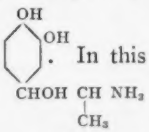
Fig. 6 (H. B.).—*A* shows an induced standstill of five and two-tenths seconds. *B*, taken one minute after the intravenous administration of 0.01 mg. of l-epinephrine, shows ventricular rhythm; the rate is 33. *D* shows the disappearance of the effect seven minutes after the injection.

It is not the purpose of the present report to discuss in detail the chemical structure of the various compounds but merely to point out the essential differences from the composition of epinephrine.

Epinephrine  is the laevo isomer of an amine consisting of a

catechol nucleus and a side chain $CHOH\ CH_2\ NHCH_3$ containing the amine group. The epinephrine substitutes are either optical or chemical isomers of epinephrine or have some alteration in the structure affecting the nucleus or the side chain or both.

Optical Isomers.—Natural epinephrine is laevorotatory, while the synthetic base is racemic. In 1908 the dextrocomponent became available for study and practically all agree that the d-isomer has a relatively weaker action. Ratios of activity on the blood pressure in experimental animals varying from 1:12 to 1:40 have been reported.[20] According to Tainter [21] the median figure is 1:20. In H. B., in three experiments 1 mg. of d-epinephrine produced a response practically identical with that obtained by 0.05 mg. of natural epinephrine, thus giving a ratio of 1:20. It is evident therefore that owing to its content of the relatively weak dextrosubstance the synthetic epinephrine is approximately one-half as effective on the heart as natural epinephrine.

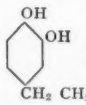
Chemical Isomers.—The only chemical isomer studied was a synthetic substance, α hydroxy β amino 3, 4 dihydroxy propylbenzene having the following structural formula:  . In this compound the methyl group which in epinephrine is bound to the nitrogen is transferred to the carbon side chain. It is stated that this compound does not produce the effect on the vagus (drop in blood pressure in animals which have not received atropine) and that it is from seven to ten times less toxic than epinephrine. It was necessary to use 0.5 mg. of this

20. Cushny, A. R.: The Action of Optical Isomers, J. Physiol. **37**:130, 1908; Further Note on Adrenalin Isomers, ibid. **38**:259, 1909. Launoy, L., and Menguy, B.: Documents numériques sur les adrenalins, droite, gauche et sur l'adrenalone, Compt. rend. Soc. de biol. **87**:1066, 1922. Fromherz, K.: Die Blutdruckwirkung des racemischen suprarenius und seiner optisch aktiven Komponenten, Deutsche med. Wchnschr. **49**:814, 1923.

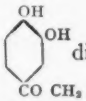
21. Tainter, M. L.: Comparative Actions of Sympathomimetic Compounds: Catechol Derivatives, J. Pharmacol. & Exper. Therap. **40**:43, 1930.

substance to obtain a response comparable to that produced by 0.05 mg. of the epinephrine, so that it is approximately one-tenth as active.

Synthetic Substances Resembling Epinephrine.—The compound



is a synthetic substance closely resembling epinephrine in chemical structure except for the absence of the hydroxyl group on the first carbon atom of the side chain. It is marketed in a 1 per cent solution as a substitute for epinephrine. Barger and Dale [19] found that the absence of the hydroxyl group in this position greatly reduced the pressor activity. Tainter [21] observed that the drug was approximately one-twelfth as active on the blood pressure of cats, and Jackson [22] reported that this substance was about one-tenth as active on the blood pressure as epinephrine. By the present method it was found that approximately forty times as much of this substance was required to produce a response comparable to that obtained by l-epinephrine.

The compound  differs from epinephrine only in having a ketone in place of the hydroxyl group in the side chain. Barger and Dale [19] found that the substitution of a ketone markedly reduced the effect on the blood pressure, and Tainter [21] observed that approximately from one hundred to two hundred times as much of this drug as of l-epinephrine was needed to cause the same pressor response in cats. By the present method 8 mg. of the substance produced a response on the ventricular rhythm comparable to that obtained by 0.2 mg. of l-epinephrine, indicating a ratio of activity to epinephrine of 1:40 (fig. 7).

Synephrin Tartrate and Neosynephrine Hydrochloride.—Synephrin tartrate is a synthetic amine which differs from epinephrine in that there is but one hydroxyl on the benzene ring so that the nucleus is a phenol instead of a catechol. The side chain is unchanged. It is more stable and less toxic than epinephrine. In the German literature this compound has been widely recommended as a substitute for epinephrine, the suggested dose being fifty times that of epinephrine. In the application of this substance to induced cardiac standstill, approxi-

22. Jackson, D. E.: The Peripheral Action of Certain Drugs, J. Pharmacol. & Exper. Therap. **4**:291, 1912.

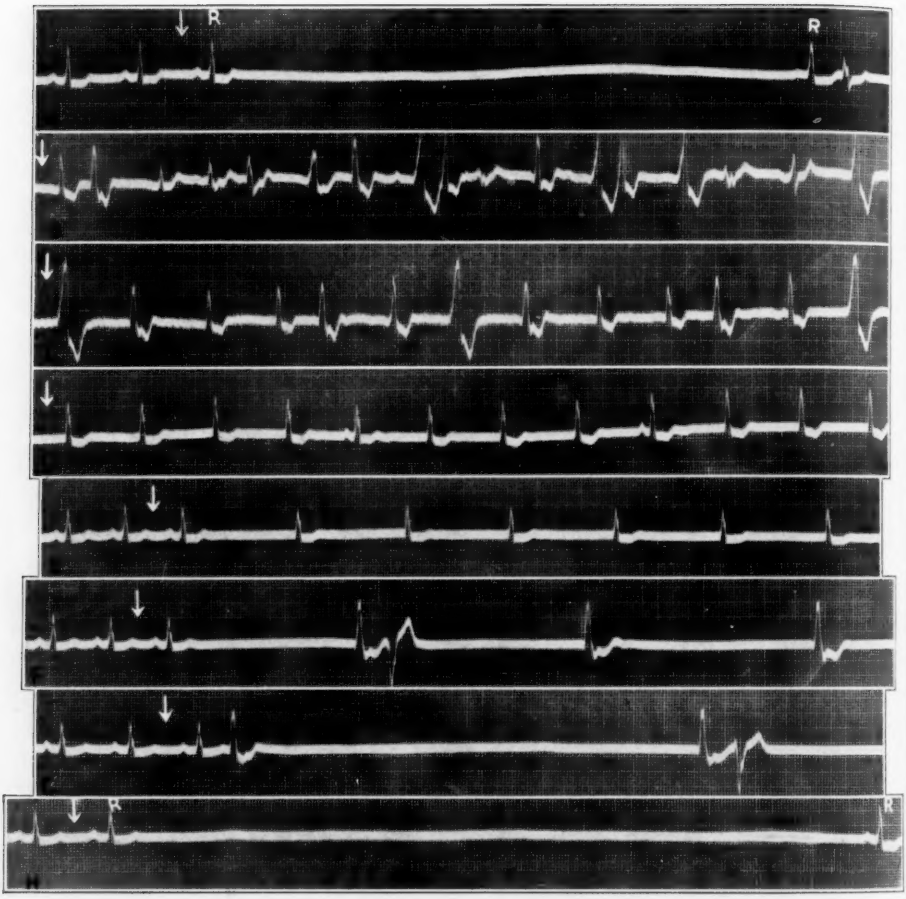
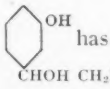
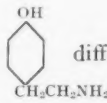
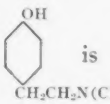


Fig. 7 (H. B.).—*A* shows an induced standstill of eight and two-tenths seconds. The lower tracings were taken after the intravenous administration of 8 mg. of a compound differing from epinephrine only in the substitution of a ketone for the hydroxyl group in the side chain. The maximum ventricular rate was 100, one minute after the injection. *H* was made twenty-five minutes after the injection. This response compares with that shown in figure 8.

mately four hundred times as much synephrin tartrate was required to produce the same effect as epinephrine.

Neosynephrin hydrochloride  has the same chemical composition as synephrin tartrate, differing only in that the hydroxyl group on the benzene ring is in the meta instead of the para position. This substance was found to be more active than synephrin tartrate. Two milligrams of neosynephrin hydrochloride, given intravenously, induced a response comparable to that of 0.02 mg. of epinephrine, indicating a ratio of 1 : 100.

Tyramine.—Tyramine  differs essentially in chemical structure from epinephrine in the absence of one hydroxyl group on the nucleus and a hydroxyl on the side chain. Tyramine was found in ergot by Barger and Dale [19] and is now prepared synthetically. The substance is not used in therapy, but Hewlett and Kay [23] showed that in normal men subcutaneous injections of 60 mg. produced a prolonged rise of the blood pressure, and they recommended its use in surgical shock. Dale and Dixon [24] considered that the action of tyramine was the same as that of epinephrine, differing merely in degree and duration of effect. Tainter,[25] however, concluded that the principal action of tyramine was direct muscular stimulation and that sympathetic stimulation was not prominent. By the present method it was found that tyramine produced qualitatively the same reaction on the heart as epinephrine. A response comparable to that evoked by 0.05 mg. of epinephrine was produced by 60 mg. of tyramine, thus giving a ratio between tyramine and epinephrine of 1 : 1,200.

Hordenine.—Hordenine  is present in the germ of malt grains and is closely related in structure to tyramine, differing only in having two methyl groups attached to the side chain. Barger and Dale [19] demonstrated that hordenine produced a very weak pressor reac-

23. Hewlett, A. W., and Kay, W. E.: The Effect of Tyramin on Circulatory Failure, J. A. M. A. **70**:1810 (June 15) 1918.

24. Dale, H. H., and Dixon, W. E.: The Action of Pressor Amines Produced by Putrefaction, J. Physiol. **39**:25, 1909.

25. Tainter, M. L.: The Action of Tyramine on the Circulation and Smooth Muscle, J. Pharmacol. & Exper. Therap. **30**:163, 1926.

tion in animals, and Jackson [26] observed that this compound was an effective bronchial dilator, but had only a slight pressor action as compared with epinephrine. Sixty milligrams of hordenine sulphate produced a response on the induced cardiac standstill somewhat less intense than that of 0.01 mg. of epinephrine, giving a ratio of approximately 1 : 6,000.

Ephedrine.—Ephedrine differs from epinephrine in chemical

structure in the absence of two hydroxyls on the nucleus and in having an additional atom of carbon in the side chain. It has been demonstrated by Barger and Dale [19] that both of these changes definitely weaken the pressor activity. Although ephedrine has been the subject of much investigation, it has not been conclusively demonstrated that it reproduces all of the physiologic reactions of epinephrine. Certain observations suggest qualitative differences in the action of the two drugs on the heart. Gradinesco [27] found that epinephrine restores the beat of a frog's heart which has been arrested by perfusion with ephedrine. La Barre [28] showed that ephedrine did not lead to ventricular fibrillation in cats under chloroform anesthesia, in which respect it differed from epinephrine. The present experiments, however, demonstrate that ephedrine increases cardiac rhythmicity in the same manner as epinephrine, differing only in degree. Chen [29] found the ratio of pressor activity of ephedrine to epinephrine to be 1 : 142. In three subjects it was possible to make a quantitative comparison of epinephrine and ephedrine by the present method. In H. B. 100 mg. of ephedrine produced a response comparable in intensity to that of 0.05 mg. of epinephrine, giving a ratio of 1 : 2,000 (fig. 8). The duration of the effect was one hour and forty-five minutes as compared with fifteen minutes for the same amount of epinephrine. It is interesting that Chen and Meek [30] found that in dogs for a certain rise in blood pressure the duration of the effect of ephedrine was also seven times greater than that of epinephrine. In two other subjects the approximate ratios were between 1 : 1,500 and 1 : 2,000. It is apparent that ephedrine has a

26. Jackson, D. E.: The Action of Drugs on Bronchioles, J. Pharmacol. & Exper. Therap. **5**:491, 1914.

27. Gradinesco, A.: Difference d'action entre l'éphédrine et l'adrenaline, Compt. rend. Soc. de biol. **96**:1027, 1927.

28. La Barre, J.: Existe-t-il une syncope éphédrino-chloroformique, Compt. rend. Soc. de biol. **98**:863, 1928.

29. Chen, K. K.: A Comparative Study of Synthetic and Natural Ephedrines, J. Pharmacol. & Exper. Therap. **33**:237, 1928.

30. Chen, K. K., and Meek, W. J.: A Comparative Study of Ephedrine, Tyramine and Epinephrine with Special Reference to the Circulation, J. Pharmacol. & Exper. Therap. **28**:59, 1926.

decidedly weaker effect on the cardiac rhythmicity than on the blood pressure as compared with epinephrine. This indicates that for the prevention of cardiac standstill ephedrine must be administered in doses larger than those ordinarily employed to raise the blood pressure.

Phenylethanolamine.—Phenylethanolamine differs essentially

from epinephrine in the absence of two hydroxyls on the nucleus. Alles [31] has synthesized this compound and studied its physiologic prop-

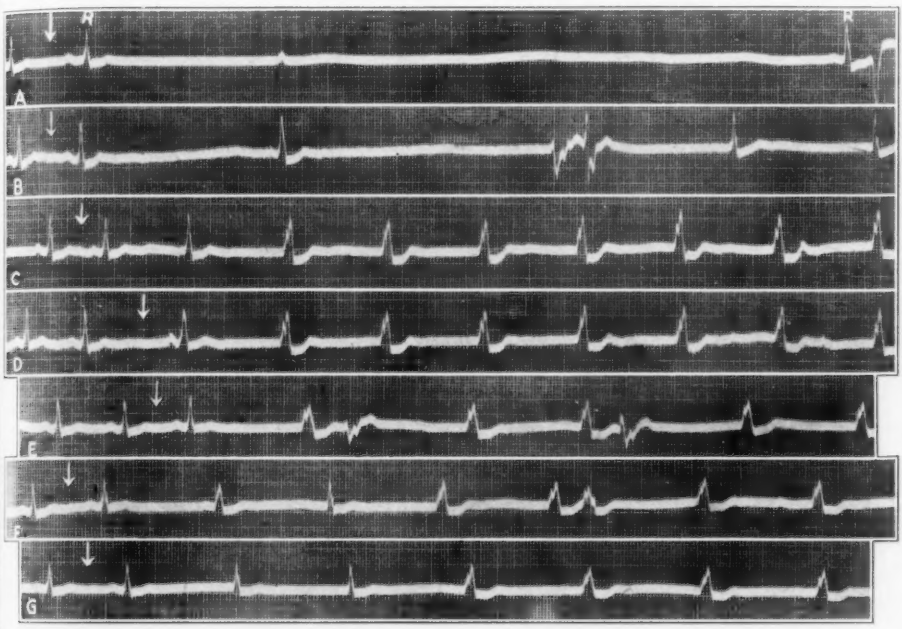


Fig. 8 (H. B.).—*A* shows induced standstill of nine and six-tenths seconds. The lower tracings were made after the administration of 100 mg. of ephedrine sulphate intravenously. The maximum rate of ventricular rhythm is 60. This response compares in intensity with that shown in figure 5.

erties and toxicity. It produces an increase in the rate and amplitude of the cardiac contraction with a definite rise in blood pressure. Tainter [32] found that phenylethanolamine had actions on the circulation

31. Alles, G. A.: Comparative Physiological Action of Phenylethanolamine, J. Pharmacol. & Exper. Therap. **32**:121, 1928.

32. Tainter, M. L.: Pharmacological Actions of Phenylethanolamine, J. Pharmacol. & Exper. Therap. **36**:29, 1929.

similar to that of ephedrine and tyramine. Miller and Piness [33] have used the drug in clinical cases and have observed slight rises in blood pressure following the subcutaneous injections of 100 mg. of the substance. In H. B. the injection of 160 mg. intravenously produced a reaction comparable to that caused by 0.02 mg. of epinephrine, giving a ratio of activity of 1 : 8,000.

Catechol.—Catechol is the nucleus of the epinephrine molecule, and Dakin [34] concluded that catechol was necessary for the production of an action of epinephrine, stating that catechol itself stimulated sympathetic nerve endings in the same manner as epinephrine. Barger and Dale,[19] however, concluded that catechol was an unessential constituent for stimulation of the peripheral sympathetic nerve, and that its action was not related to that of epinephrine. The injection of 200 mg. of catechol intravenously was without effect on the induced cardiac standstill, confirming the conclusion of Barger and Dale that this substance does not possess a sympathomimetic action.

COMMENT

Information regarding the effectiveness of drugs on cardiac standstill in man has been derived from two sources: (1) the response of the asystolic heart to various intracardiac injections, and (2) the effect of drugs in the prevention of the Adams-Stokes seizures of heart block. The conclusions from these sources are open to objection since resuscitation by intracardiac injection may be due in part to the mechanical stimulation of the needle puncture. There is also a spontaneous variation in the frequency of the Adams-Stokes seizures of heart block, so that a favorable response cannot safely be attributed to the administered drug. A large variety of compounds unrelated in chemical composition or in physiologic action have been employed, and in many instances favorable results have been reported. This has led to the suggestion that the response of the heart is no specific for any pharmacodynamic action.[14]

By the present method the action of a drug on cardiac standstill can be observed under controlled conditions and the effectiveness estimated quantitatively. The results indicate that many substances which are used in the prevention and treatment of cardiac standstill are entirely inactive. For example, digitalis is administered as an emergency mea-

33. Miller, H., and Piness, G.: A Synthetic Substitute for Ephedrine, J. A. M. A. **91**:1033 (Oct. 6) 1928.

34. Dakin, H. D.: On the Physiological Activity of Substances Indirectly Related to Adrenalin, Proc. Roy. Soc. London, s. B **76**:493, 1905.

sure in cardiac arrest such as occurs during a surgical operation. The present observations indicate that a single dose of digitalis cannot stimulate cardiac rhythmicity and is therefore ineffective. Actually this drug may be distinctly harmful, tending to prevent the spontaneous return of the rhythmic function.

Comparative Effects on Cardiac Standstill of Compounds Related to Epinephrine

Drug	Structural Formula	Approximate Ratio of Activity to l-epinephrine
l-epinephrine		1:1
d-epinephrine		1:20
∝hydroxy Aamino 3,4 dihydroxy propyl-benzene		1:10
Synthetic Substance		1:40
Synthetic Substance		1:40
Neosynephrin hydrochloride		1:100
Synephrin tartrate		1:400
Tyramine		1:1,200
Hordenine		1:6,000
Ephedrine		1:1,500 - 1:2,000
Phenylethanolamine		1:8,000
Catechol		Ineffective

The compounds were in the following forms: l-epinephrine, ∝hydroxy Aamino 3,4 dihydroxy propylbenzene and the first-mentioned "Synthetic Substance" as hydrochlorides; d-epinephrine as the bitartrate; tyramine and hordenine, ephedrine and phenylethanolamine as the sulphates.

The activity of the various sympathomimetic amines suggests that the response of the heart is the result of a specific pharmacodynamic action, namely, stimulation of the cardiac accelerator mechanism, and only drugs possessing this action are likely to be effective on cardiac standstill.

In the application of the present observations to the therapy of cardiac standstill it is apparent that natural epinephrine is the most

active substance, but it is of some importance that a number of related compounds will produce the same effect if administered in the proper dose (table). The disadvantages usually attributed to epinephrine are its transitory action and ineffectiveness on oral administration. This is not objectionable in the treatment of a stopped heart, since an acute effect is sufficient and the drug must necessarily be injected into the heart. However, in the prevention of cardiac asystole, such as may occur in heart block, these features of the action of epinephrine may limit its usefulness. It was found in the present study, however, that the action of epinephrine on cardiac rhythmicity is not as transitory as has been indicated from the observation of reactions on the blood pressure. Whether the drug was administered by the subcutaneous, intramuscular or intravenous route, it was found repeatedly that the duration of the prevention of standstill was five times that of the rise in blood pressure. It was also repeatedly demonstrated that the effects of shorter duration, such as one hour, could be definitely prolonged by massaging the site of the injection, as first suggested by the observations of Luckhardt and Koppanyi.[35] It appears, therefore, that in cases of heart block in which the syncopal attacks are relatively frequent, epinephrine is the drug of choice and that a subcutaneous injection every three or four hours should maintain an increased ventricular rhythmicity sufficient to prevent a standstill.

In cases of chronic heart block with a slow ventricular rate and infrequent syncopal attacks, a drug which would be effective by oral administration is desirable. The effects of several of the compounds which were effective on intravenous injection were studied after oral administration. Epinephrine administered in oral doses as high as 30 mg. was ineffective, indicating the completeness of its destruction, when it is realized that 0.01 mg. was effective by intravenous injection. α hydroxy β amino 3, 4 dihydroxy propylbenzene, although definitely active in doses of 0.5 mg. administered intravenously was without effect in doses of 30 mg. given orally. Neosynephrin hydrochloride, which prevented cardiac standstill in doses of 2 mg. intravenously, was ineffective in oral doses of 50 mg. every four hours. One hour after a single oral dose of 180 mg. a prolonged cardiac standstill could be induced. Phenylethanolamine, which has not been used previously in the therapy of heart block, prevented cardiac standstill in doses of 250 mg. by mouth, so that this drug deserves a trial in the treatment of this condition. Ephedrine administered orally, was ineffective in H. B. in doses of 100 mg. One hour after 250 mg. of ephedrine sulphate had been given by mouth, however, pressure on the carotid sinus resulted in a ventricular rhythm comparable to that obtained from the intravenous administration

35. Luckhardt, A. B., and Koppanyi, T.: Studies on the Hemodynamic Action of Subcutaneously Injected Epinephrin, Am. J. Physiol. **81**:436, 1927.

of 100 mg. It is improbable that such large amounts are ordinarily necessary. The comparative insensitiveness of this patient to ephedrine is indicated by the fact that 50 mg. intravenously was inactive, while in two other subjects this amount produced a definite effect.

It is unfortunate that the more effective substances are not sufficiently stable to withstand the action of digestive ferments. At present it appears that there are only two sympathomimetic substances, ephedrine, and phenylethanolamine, which definitely increase ventricular rhythmicity on oral administration. It is probable that comparatively large doses will be necessary, up to 150 mg. of epinephrine and 250 mg. of phenylethanolamine, for the prevention of cardiac standstill. It is apparent that further progress in the therapy of chronic heart block lies in the direction of the development of more stable compounds having a higher sympathomimetic activity.

SUMMARY

1. In certain persons the activity of the cardiac pacemaker may be temporarily eliminated and an arrest of the heart induced by pressure on the right carotid sinus.

2. In eight cases studied the subcutaneous injection of epinephrine abolished the standstill by stimulating a new center of impulse formation in the ventricles.

3. Ephedrine administered intravenously produced a similar response in three cases.

4. Barium chloride by mouth abolished the cardiac standstill in a similar manner in one case and was ineffective in another.

5. Calcium gluconate, caffeine sodium benzoate, coramin metrazol and thyroxine were without effect in a subject who responded consistently to epinephrine.

6. Digitalis prolonged the period of induced cardiac standstill.

7. A group of compounds chemically related to epinephrine produced in a varying degree a reaction similar to that of epinephrine.

8. The ratios of activity of these compounds as compared with epinephrine were estimated.

9. The effectiveness of the epinephrine-like compounds indicates that in the therapy of cardiac standstill a specific pharmacodynamic action is required, which is the stimulation of the cardiac accelerator mechanism.

10. Epinephrine is the most active drug in the treatment of the stopped heart and in the prevention of the frequent syncopal attacks of chronic heart block.

11. Ephedrine and phenylethanolamine in large doses are effective by mouth and are applicable in certain cases of heart block.

Dr. Arthur D. Hirschfelder of the Department of Pharmacology assisted in this work with helpful suggestions.

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DISCUSSION

DR. ARTHUR D. HIRSCHFELDER, Minneapolis: In this series of observations Dr. Nathanson has opened up a new avenue for the study of the properties of the human ventricle which is beating independently and for a quantitative study of the relative activities of various drugs. His studies have shown the relations that exist between effects on vasoconstriction and effects on ventricular rhythmicity, and these will certainly be of great practical applicability. Few clinical studies, except the classic studies of His and of Erlanger on heart block are comparable to them in thoroughness and in beauty of execution. The relative activities of the drugs of the epinephrine and ephedrine series and the relation of the chemical constitution to the actions in clinical cases which Dr. Nathanson has presented so closely resemble the observations previously made in experiments on animals (Barger and Dale, Chen, Tainter and others) that they will certainly lead to the development of new standards of comparison and to more certain clinical therapy, which further studies along these lines will probably confirm and render more definite.

MORPHOLOGIC VARIETIES OF BRONCHIECTASIS IN THE ADULT

THEIR PROBABLE PATHOGENESIS AND CLINICAL DIFFERENTIATION

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Pathologists have long described various forms of bronchial dilatation, such as cylindric, globular and saccular, but until recently no attempt was made to differentiate these bronchiectatic forms clinically. The introduction of iodized poppy-seed oil 40 per cent as a safe diagnostic means in the roentgenologic exploration of the bronchial tree made it possible to visualize and study the various morphologic types of bronchiectasis in the living and has led to an almost complete revision of the hitherto accepted views on the clinical aspects of the condition. Studies by Bezançon, Weil, Azoulay and Bernard,[1] Reinberg[2] and others have definitely established the fact that marked bronchiectasis may exist without bronchorrhea or cough, and that the amount of bronchial secretion bears no causative relation to the development of bronchial dilatation. Gauthier,[3] Sergent and Jobin[4] and others have drawn attention to the widely divergent ways in which bronchiectasis may manifest itself and to the variable clinical course which it may pursue. Ballon and Ballon[5] described a roentgenologic classification of bronchiectasis without, however, correlating the various forms with their clinical features.

The roentgen images of bronchiectasis as outlined with iodized oil are multiform and have been variously described as: cylindric, saccular, globular, clubbing, beaded, varicose, fusiform, like a pigeon's nest, a raisin seed or fingers of a glove, etc. Some of the terms could no doubt be used synonymously, and some of the forms when analyzed properly

1. Bezançon, Weil, Azoulay and Bernard: Forme sèche hemoptoique de la dilatation des bronches, Presse méd. **15**:157 (Feb. 20) 1922.

2. Reinberg, S. A.: Roentgen-Ray Studies on the Physiology and Pathology of the Tracheobronchial Tree, Brit. J. Radiol. **30**:451, 1925.

3. Gauthier, G.: Contribution à l'étude de formes larvées de la dilatation des bronches chez l'adulte, Thèse de Lyon, 1925.

4. Sergent and Jobin: Les images radiologiques dans les formes fétides et nonfétides de la dilatation des bronches, Bull. Acad. de méd., Paris **99**:582 (May 29) 1928.

5. Ballon, D. H., and Ballon, H. C.: Pneumonography with Iodized Oil, 40 per Cent, by the Bronchoscope Method, Arch. Surg. **14**:184 (Jan.) 1927.

from the pathogenic and clinical point of view would prove to be subvarieties or evolutive stages of the same type. We have attempted to classify into six definite varieties the numerous cases of bronchiectasis which we observed at the Cumberland Hospital and Clinic, at the Pulmonary Clinic of the Post-Graduate Hospital (Bendove) and in our private practice. The classification includes five morphologic types of bronchiectasis and one of bronchiolectasis, each of which is characterized by a more or less distinctive clinical syndrome and is considered to be the result of different pathogenic factors both structural and functional. In a previous contribution,[6] we discussed fully the physiopathologic changes which may precede or accompany the ectatic condition of the bronchus, and we indicated the diagnostic significance of these impaired functions in the early stages of the several forms of bronchiectasis. Before describing the morphologic appearance of each bronchiectatic variety, we find it pertinent to review briefly the recent contributions on the respiratory and expulsive functions of the bronchi which have thrown new light on the pathogenesis of bronchiectasis in general.

PATHOLOGIC PHYSIOLOGY OF ECTATIC BRONCHI

Studies by Reinberg,[7] Macklin,[7] Miller,[8] Bullowa and Gottlieb [9] and others have yielded many new facts regarding the respiratory dynamics of the bronchi and their elaborate protective or expulsive mechanism. The physiologically functioning bronchi are not merely conducting tubes for distributing air to, and collecting it from, the alveoli but are actively participating in the process of pulmonary inflation and deflation. The respiratory movements of the bronchi consist of an inspiratory elongation with widening of the caliber and an expiratory shortening with constriction of the caliber. The structure of the bronchial wall is admirably adapted to these rhythmic changes in length and width, which are synchronous with the respiratory phases (Miller and Macklin). Pathologic processes which involve the fibro-elastic or myo-elastic layers of the bronchus render it more or less stiff and hinder its respiratory function. Rigid bronchi of this sort can be studied clinically by intrabronchial instillation of radiopaque substances, and Bonnamour, Badolle

6. Bendove, R. A., and Gershwin, B. S.: The Inverse Ratio in the Roentgenologic Visualization of the Bronchi and Alveoli After the Injection of Contrast Media, Am. J. Roentgenol. **31**:323 (March) 1934.

7. Macklin, C. C.: The Musculature of the Bronchi and Lungs, Physiol. Rev. **9**:1 (Jan.) 1929.

8. Miller, W. S.: Key Points in Lung Structures, Radiology **4**:173, 1925; Musculature of Bronchial Tree and Its Relation to Certain Pathologic Conditions, Am. Rev. Tuberc. **5**:689, 1921.

9. Bullowa, J., and Gottlieb, C.: Experimental Studies in Bronchial Function, Laryngoscope **32**:284 (April) 1922.

and Gaillard[10] described this phenomenon as the "lipiodoradiologic syndrome of bronchial immobilization" which is present in cases of chronic bronchitis and early bronchiectasis (figs. 1 *A* and 5 *B*).

The involvement of the myo-elastic layers of the bronchus results not only in diminution of its respiratory function but also in the decrease of its evacuative capacity, though the latter depends on other factors as well. The bronchi are endowed with an efficient threefold expulsive mechanism: the cough reflex, the action of the cilia and a progressive wavelike motion said to resemble peristalsis. The bechic reflex, according to Reinberg and others, functions best in the trachea and primary bronchus, diminishes in intensity in the secondary and tertiary bronchi

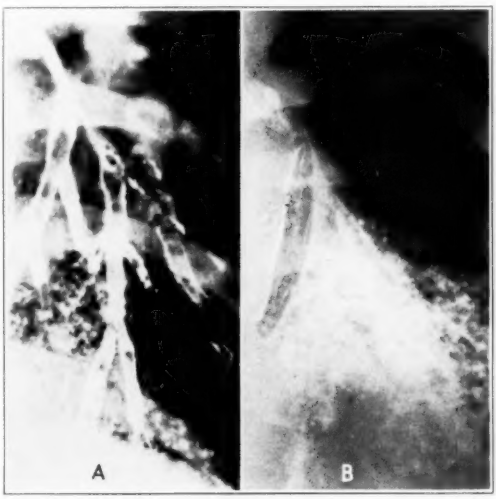

Fig. 1.—*A*, tubular type of bronchiectasis; the walls of the bronchi are lined with iodized oil, but the lumen is empty, giving the bronchi an appearance of hollow or "macaroni" tubes. *B*, a fusiform subvariety of the tubular dilatation in the inner zone of the lower lobe.

and is absent in the rest of the bronchial tree as well as in the pulmonary parenchyma. Hence, even an extensive peripheral lesion may not cause cough until the inflammatory exudate reaches the bronchi of the first and second order. The cilia which line the entire airway as far as the terminal bronchioles are able to waft up only small irritating particles, and their action becomes easily attenuated by a catarrhal condition. The peristaltic movements were studied experimentally by Reinberg[2] and

10. Bonnamour, S.; Badolle, A., and Gaillard, R.: Le radio-diagnostic dans les affections broncho-pulmonaries par le lipiodol, Paris, L'expansion scientifique française, 1929.

Hudson and Hane [11] and were found to be present in the entire tract, including even the airway terminals. This expulsive phenomenon is dependent mostly on the bronchial musculature, though the integrity of the mucosa and the sensory nerve endings found therein is also essential for the proper reflex stimulation. Pathologic involvement of any of these bronchial coats will result in a lessening of the evacuative capacity of the bronchus in question, the degree of functional diminution bearing a relation to the extent and type of lesion and the particular bronchial layer thus affected.

Our observation, which was fully described in a previous contribution,[6] that a physiologically functioning bronchus rids itself of the injected iodized oil in about twenty minutes, is in accord with that of Bonnamour, Badolle and Gaillard.[10] A bronchus which remains filled with the instilled oil at the end of that period is to be considered a retentive bronchus, the walls of which are either structurally changed or physiologically insufficient. The functional impairment of the bronchus will manifest itself before true ectasia can be detected, and the diagnostic significance of this functional test in early bronchial involvement deserves further study. A definitely ectatic bronchus, irrespective of its location, shows a great tolerance toward the injected substances and in certain morphologic types the iodized oil can be found in the bronchus days or even weeks after the injection.

MORPHOLOGIC CLASSIFICATION OF BRONCHIECTASIS AND THE PROBABLE PATHOGENESIS OF EACH TYPE

It must always be kept in mind that ectasia proper is only one manifestation of the multifarious pathologic changes which are brought about in the layers of the bronchial wall by different etiologic factors. The pathologic process may start primarily in the mucosa of the bronchi or in the muscular and elastic layers, or it may originate in the pulmonary parenchyma, implicating the bronchial coats subsequently. These mural changes may be inflammatory, degenerative, sclerotic or suppurative and may involve one or more bronchi at the same time. All of the various pathogenic factors, singly or jointly, determine the resultant ectatic configuration, which can be clearly visualized in vivo by means of intrabronchial injection of a contrast medium such as iodized oil.

We differentiated six morphologic types of bronchial dilatation, five of which are bronchiectasis and one of which is bronchiolectasis. They are: the tubular, cylindric, varicose and globular types, bronchiolectasis and bronchiectatic abscess.

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11. Hudson, W. A., and Hane, H. A.: Camera Studies of the Tracheobronchial Tree, Arch. Surg. **19**:1236 (Dec.) 1929.

Tubular Bronchiectasis.—When the dilated bronchi of the tubular form are outlined with iodized oil, they appear like hollow cylinders or tubes; i. e., the walls of the bronchi are lined with the injected material, while the lumen remains empty (fig. 1 *A*). The bronchial mucosa is always involved in this type of ectasia, and the injected material adheres to the diseased membrane, imparting to the bronchi the appearance of empty tubes or "macaroni tubes" (Rosenthal). Catarrhal or inflammatory conditions of the mucosa are, as a rule, the starting pathologic process, with involvement of the other bronchial coats and resultant ectasia. The mucosa of several bronchi may be affected, and the diminution of functional capacity depends on the degree of involvement of the other bronchial coats. The dilatation is, as a rule, uniform in diameter, but a localized constriction in any part of the bronchi caused by accumulated secretion may give rise to fusiform or conical subvarieties of tubular bronchiectasis (fig. 1 *B*). Many French clinicians have stated that this form of bronchial dilatation is always encountered in soldiers who were gassed in the World War; they call it "bronchial dilatation of the gassed" (Bonnamour, Badolle and Gaillard). However, continuous irritation of the bronchial mucosa is likely to give rise to this form of bronchiectasis, and it often follows repeated attacks of bronchitis. Laennec's [12] theory that bronchiectasis is always caused by stagnant bronchial secretions would fit this type of ectasia well, but it would in no way explain the mechanism of production of other forms of bronchial dilatation in which bronchorrhea is absent.

Cylindric Bronchiectasis.—A common type of bronchial dilatation is the cylindric form (fig. 2 *A*). When the ectatic bronchi are filled with iodized oil, they look like solid cylinders extending sometimes as far as the periphery of the lung but usually terminating abruptly in any portion of the lobe. As a rule, little alveolar tissue is outlined in the corresponding territory, and the bronchi which are filled with the iodized oil resemble the dry, leafless branches of a tree in winter. The morbidly dilated bronchi have lost much of their resilience as a result of degenerative and sclerotic changes in the myo-elastic layers. The analogous anatomic arrangement of the bronchial and arterial systems has been mentioned by many, and the factors which render the arterial wall vulnerable to sclerosis are no doubt responsible for the sclerotic changes of the bronchial walls, which eventually yield to the constant intrabronchial strain and stress and become permanently and uniformly dilated. Stokes' [13] description of paralysis of the circular muscle and

12. Laennec, R. T. H.: Traité de l'auscultation médiate et des maladies des poumons et du cœur, Paris, J. A. Brosson & J. S. Chaudé, 1819.

13. Stokes, W.: Treatise on Diagnosis and Treatment of Diseases of the Chest: Part I. Disease of the Larynx and the Windpipe, Dublin, Hodges and Smith, 1837.

loss of contractility of the bronchi and Andral's [14] suggestion that the nutritional changes in the bronchial wall may precede bronchiectasis could be applied to this type of dilatation.

Many subvarieties of the cylindric type of bronchiectasis are encountered: aneurysmal-like pouching, tapering of the distal or proximal end or of both ends of the same bronchus, medial constriction of the bronchial lumen and other morphologic mutations engendered by local inflammatory conditions and mechanical forces. Figure 2 *B* shows a general cylindric type of bronchiectasis of the left lower lobe, one bronchus of which appears markedly dilated, with extreme narrowing of the distal

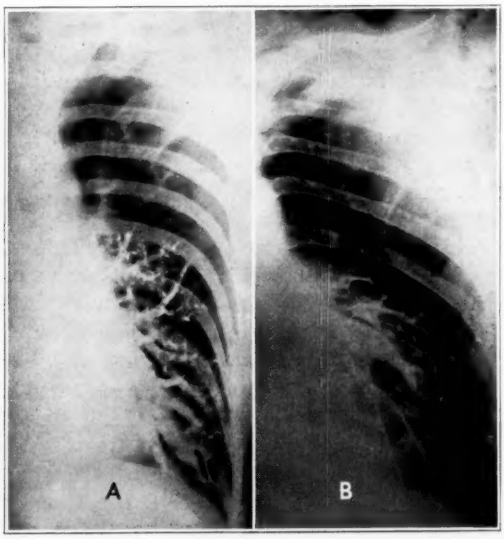

Fig. 2.—*A*, cylindric form of bronchiectasis; note that the ectatic bronchi, filled with iodized oil, appear like solid cylinders extending in various directions. *B*, conical subvariety of cylindric dilatation with tapering toward the distal end; this type is easily drained.

end, which gives it a conical appearance. Drainage is, as a rule, facilitated in this type of ectasia, but when constriction occurs at the middle or proximal end of the bronchus, drainage is much hindered. However, it should be stressed that the cylindric dilatation per se does not cause bronchorrhea, unless secondary inflammatory conditions set in.

Varicose Bronchiectasis.—Certain ectatic bronchi into which injections of iodized oil have been made look like swollen, knotted and tortu-

14. Andral: Medical Clinic, translated by D. Spillan, Philadelphia, E. Barrington & G. D. Haswell, 1843.

ous cords which sometimes stretch from the trachea to the smaller bronchioles (fig. 3*A*). This type of bronchiectasis is always found in cases of pulmonary fibrosis, and the distortion of the bronchi is no doubt due to the irregular traction on the bronchial wall by the cicatrizing parenchyma. The pathogenesis of this type of bronchiectasis is in accord with the theory advanced about a century ago by Corrigan,[15] that cirrhosis of the lung is responsible for the dilatation of the bronchi. It is obvious that this theory cannot be applied to all other types of bronchietasis which show only a nominal or no pulmonary fibrosis. However, in cases of pulmonary cirrhosis, irrespective of the cause, it is plausible to consider the contraction of the cirrhotic parenchyma as the dominant factor in producing distortion and dilatation of the bron-

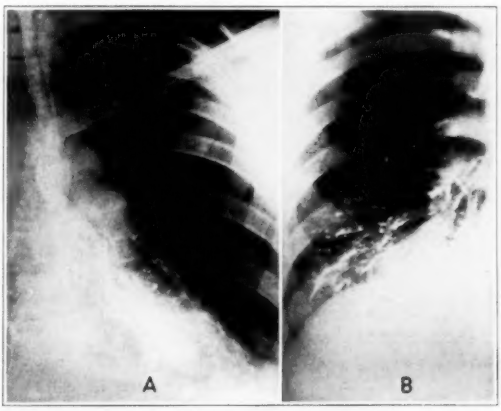

Fig. 3.—*A*, varicose type of bronchiectasis; the bronchi, filled with iodized oil, look like knotted and tortuous cords. The trachea, deviated to the left, is also outlined. *B*, bronchiolectasis; note the ectatic bronchioles filled with iodized oil; the bronchi appear to retain their normal caliber. Both of these forms of ectasia are the result of pulmonary fibrosis.

chi in its corresponding territory. This form is encountered in pulmonary tuberculosis, atelectasis, pleuritic adhesions, pneumonitis and similar conditions.

Bronchiolectasis.—Pathogenetically, bronchiolectasis belongs to the type of varicose bronchiectasis; i. e., it results from pulmonary fibrosis and atelectasis, but because of its different topographic distribution and morphologic aspect as well as clinical features it is considered to be in a class by itself. The dilated bronchioles filled with iodized oil are clustered around the empty bronchi, which seem to retain their normal

15. Corrigan, D.: Dublin J. M. Sc. **13**:266, 1838.

anatomic width (fig. 4 *B*). Sometimes the bronchi are not outlined by the injected contrast medium, and only the ectatic bronchioles are visualized. Influenza, bronchopneumonia or other pulmonary lesions of bronchial distribution are the precursors of bronchiolectasis. The diffused fibrosis and atelectasis around the terminal bronchioles produce a dilatation of the bronchioles which may be unilobular, unilateral or bilateral.

Globular or Ampullar Bronchiectasis.—In a relatively small number of cases, the iodized oil reveals minute globules or capsules filled with fluid scattered throughout the area into which the injection had been made or suspended from the bronchial stem and resembling a bunch of grapes or scattered raisin seeds (fig. 5 *A*). Many French clinicians are

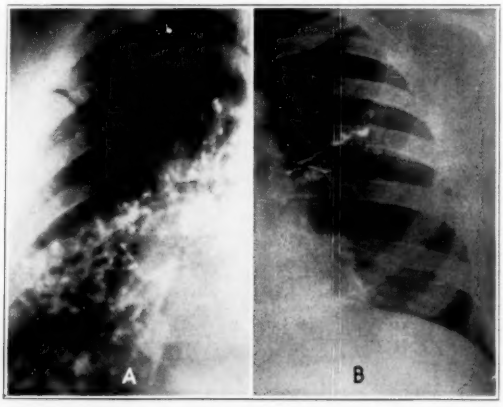

Fig. 4.—*A*, globular or ampullar type of bronchiectasis. Note the numerous globules or capsules, partially or completely filled with iodized oil, scattered throughout the pulmonic field like raisin seeds. *B*, two ectatic segments outlined with iodized oil protrude from the bronchial wall like two cups filled with fluid.

of the opinion that this type of bronchiectasis is usually of syphilitic origin, and they recommend antisyphilitic treatment, even if the Wassermann reaction is negative. It is possible that syphilitic lesions of the bronchi are a frequent factor in the production of this form of ectasia. However, bronchial ulcer of another pathogenesis cannot be excluded. Localized abrasion of the bronchial mucosa may lead to an ulcerative process which gradually penetrates the other layers of the bronchial wall at that point, causing the wall to yield to the constant respiratory stress; the result is localized swelling or segmental dilatation. Figure 5 *B* shows two apparently recent ulcers filled with iodized oil, which protrude from the bronchial wall like two cups filled with fluid. The only symptom complained of by this patient was recurrent slight

hemoptysis which lasted a few minutes and which could be explained by the repeated penetration of the ulcers into a small blood vessel or capillaries. This would correspond to the syndrome described by Bezançon and others in their discussion of dry hemoptic bronchiectasis, characterized by the "existence of small capsules often grouped in pairs or threes, which show a level line of the injected" iodized oil.

Primary Bronchiectatic Abscess.—The cavity of a bronchiectatic abscess may assume any shape or form; it may be multilocular and is usually visualized on the roentgenogram without the use of contrast mediums. Lilienthal [16] expressed the opinion that it usually follows operations for the removal of tonsils and adenoids. Figure 5*A* shows

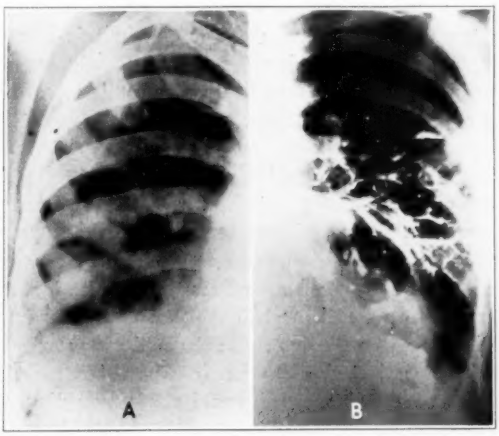

Fig. 5.—*A*, multiple bronchiectatic abscess in the right lower lobe. *B*, an irregular bronchiectatic cavity filled with iodized oil in the left lower lobe; note also the "immobilized" bronchi of normal caliber in the upper lobe retaining the injected oil.

many irregular shadows in the lower pulmonic field which were disclosed by postmortem exploration to be bronchiectatic cavities filled with pus and linked together by intercommunicating bronchial cavities. When the suppuration is preponderantly in the parenchyma, it may cast a homogeneous shadow on the roentgenogram which conceals the underlying bronchial excavation, and only by means of iodized oil is one able to delineate the extent of a bronchiectatic cavity of this nature (fig. 5*B*).

It should be strongly emphasized that any morphologic type of bronchiectasis may become suppurative, but that the suppuration is

16. Lilienthal, H.: Thoracic Surgery, Philadelphia, W. B. Saunders Company, 1925.

always a late complication evoked by the invasion of pyogenic organisms, aerobic or anaerobic, into the diseased and ectatic bronchi. The clinical course of infected bronchiectasis of this sort may then simulate that of a primary bronchiectatic abscess and may even present all of the grave sequences and sequelae. However, if no secondary infection has taken place, each morphologic type of bronchial dilatation exhibits a more or less distinctive clinical syndrome which is of diagnostic significance in early cases.

We have not included in this classification the bronchiectasis which may follow stenosis of the bronchi caused by extrabronchial pressure, as from aneurysm or mediastinal neoplasm, or by new growth of the bronchial wall. The clinical picture in cases of this sort is usually dominated by the primary lesion, and the bronchiectasis is only a complicating feature. Neither have we included in this classification the congenital types of bronchiectasis which are frequently found in children and have been fully described by pediatricians in this country and abroad. They form a category by themselves.

CLINICAL CONSIDERATIONS

The divers modes of onset and the variable clinical course of bronchiectasis have been grouped by Gauthier [3] into the following clinical forms: the pseudobronchial, the pseudotuberculous, the dry form of Bezançon and the idiopathic form of Bard; to these he adds what he calls the "larval" forms of bronchial dilatation, which have no characteristic semeiology and which are revealed only by roentgen rays and iodized oil. This clinical classification is a useful attempt at systematizing the various ways in which bronchiectasis may divulge itself, but it does not take into account the factors which bring about these clinical variations. Bonnamour, Badolle and Gaillard discussed the close association between the etiologic factors, the morphologic appearance and the clinical varieties of bronchiectasis. They described the ampullar, hollow cylindric and solid cylindric types; the first two types they considered to be distinct clinical entities, and in the third type they included all kinds of cylindric dilatation which, they claimed, cannot as yet be differentiated. We find that each of the six morphologic types described previously has its corresponding clinical syndrome, which if not pathognomonic is always indicative of the ectatic condition.

The tubular type of bronchiectasis is revealed primarily through the bronchorrhea. The cough is usually moderate but continuous, and the mucoid or mucopurulent secretion is expectorated with ease and always in small quantities. The sputum is never purulent or foul-smelling. Paroxysmal coughing on lying down is sometimes complained of; this is probably occasioned by the trickling down of secretion from the nasopharynx into the tracheobronchial tree. A history of repeated nasopharyngeal catarrh, of prolonged exposure to inorganic dust and

irritating substances or of being gassed in the World War is of diagnostic importance. Constitutional disturbances rarely occur. Physical signs are of diagnostic value rather by their absence than by their presence; rhonchi may be scattered throughout the chest. The ordinary roentgen plate shows no distinctive pathologic condition. Bronchography is as yet the most important diagnostic criterion of this type of bronchial dilatation.

The clinical syndrome of the cylindric type of bronchial dilatation varies with its distribution and particularly with the evolutive stages of the ectasia. The patient is unable to recollect a striking feature of the onset, which is as a rule insidious. Dyspnea is one of the early symptoms, increasing in intensity with the further augmentation of the bronchiectatic condition. Cough may be absent in the early stages, but it is a distressing symptom in the late stages, when the ectatic bronchi become the seat of bacterial invasion. The cough is usually fitful, being most tumultuous in the morning when the expectoration is most abundant. The physiologically weakened bronchiectatic cavity is tolerant to the secretion, which accumulates gradually until the level of a healthy bronchial region is reached and an evacuative cough is initiated. Sometimes a sudden change in position will induce a fit of coughing which may be explained by the sudden spilling over of secretion from an anesthetic bronchial area into a sensitive bronchial region in which a cough reflex is easily elicited. The sputum may be purulent; in the fusiform subvariety of ectasia sputum is expectorated with great difficulty. In cases of this sort the drainage is poor, and the retained sputum frequently becomes obnoxiously fetid. The retention of sputum may cause fever for a few days, but this will subside after drainage is established. Sometimes the sputum is blood-tinged, and it may be the most significant complaint in early cases of cylindric dilatation, even before catarrhal or suppurative changes have occurred in the bronchial wall. Clubbed fingers are invariably present in the late stages. Physical signs are not typical; there may be dulness on percussion over the ectatic areas when they are filled with secretion, the breath sounds are somewhat altered, and crepitant râles are numerous over and around the ectatic lesion. Cavernous breath sounds may be elicited, particularly in the fusiform and saccular subvarieties. In the early stages of cylindric dilatation adventitious signs may not be elicited. The exact topography and the morphologic subvariety are not revealed by ordinary roentgenology.

The symptoms of the varicose type of bronchiectasis are usually submerged under those of the concomitant pulmonary disease which antedates the ectasia. There is pulling in all directions by scar tissue around the bronchus, which distorts the shape and interferes with the evacuative capacity of the bronchus. Suppurative changes taking place in a bronchus of this nature may stimulate bronchiectasis of the suppurative cylindric type or a bronchiectatic abscess. Pain, which is rather a

rare symptom in all other varieties of bronchiectasis, may be complained of in the varicose type as well as in bronchiolectasis. The physical signs are dominantly those of the associated pulmonary lesion, which is as a rule unilateral. Roentgenograms disclose pulmonary involvement, fibrosis and a retraction of the mediastinal structures to the affected side.

The foreground of the clinical picture and the bulk of the physical signs in bronchiolectasis are composed mostly of the pulmonary involvement, which, as a rule, ushers in the condition. A bronchopneumonic disease which, irrespective of its causative agent, lasts for a long time should be suspected of being bronchiolectasis. The cough is, as a rule, hacking, and the expectoration is scanty, usually consisting of tiny rounded masses of sputum. Shortness of breath is noticed, and vague pains in the chest are a frequent complaint. The physical signs are inconclusive, though the character of the râles is more or less distinctive; no râles are heard on ordinary inspiration, but showers of fine râles are elicited over scattered areas of the chest after cough. Roentgenograms may show little deviation from the normal pulmonary roentgenogram.

The globular type of bronchiectasis may betray itself clinically by a sudden severe hemoptysis. It may produce no other recognizable clinical signs, or if infection develops in the diseased bronchial area, it may simulate another type of bronchiectatic dilatation. Small hemoptyses may recur frequently. The general condition of the patient is usually well preserved. Neither physical signs nor roentgenologic findings are of diagnostic aid in this type of ectasia. Ectasia of this sort can be individualized only by means of bronchography.

The symptom complex of the bronchiectatic abscess may resemble that of an acute pulmonary abscess or pursue a subacute course with fever, general malaise, lassitude, anorexia, loss of weight and other symptoms. Physical signs change with the vacuity or fulness of the cavity. Roentgenograms reveal single or multiform dense shadows of irregular shapes; sometimes an ill defined cavity may be outlined, particularly if the roentgenogram is taken immediately after drainage, which is rarely complete.

It is often difficult to differentiate between a primary bronchiectatic abscess and other types of bronchial dilatation on which suppurative changes have supervened, but a careful analysis of all clinical antecedents and delineation of the affected bronchi with a contrast medium will greatly facilitate the diagnosis.

The extent of the lesion can never be judged from semeiology alone. Even a large cavity may lack most, if not all, of the signs of cavitation mentioned in the standard textbook. One of us (Bendove [17]) discussed fully the mechanism and diagnosis of silent cavities of this sort which may be either absolutely mute, betraying no signs whatsoever, or rela-

tively silent, yielding none of the classic cavernous findings but manifesting other adventitious signs. The early cylindric and globular types are, as a rule, absolutely mute to physical examination, whereas all of the other types are relatively silent, with variable auscultatory signs according to the emptiness or fulness of the cavity, the resilience of the bronchiectatic wall, the uniformity of the caliber and the condition of the surrounding pulmonary tissue.

It should be emphasized that no diagnosis of bronchiectasis is complete unless the location, the distribution and, above all, the type, have been determined, for on this information often depends the therapeutic procedure to be followed. Thus we find that the therapeutic injection of iodized oil is useful in the tubular and early cylindric types, though in the latter iodine medication by mouth or hypodermically is also effective, particularly in combination with a bismuth preparation. In all other forms of bronchiectasis, iodized oil is of doubtful therapeutic value. Ochsner [18] treated a large group of patients with repeated therapeutic injections of iodized oil and found in about 32 per cent complete relief of all symptoms, but he did not state which type of bronchiectasis responded best. Statistical data on the results of treatment in bronchiectasis have little value if the type of the ectasia is not taken into consideration, for unequal elements may thus be compared.

Postural drainage is easily accomplished in the cylindric type, particularly if the dilatation is in the larger bronchi, but it is difficult to evacuate the fusiform and sacculated subvarieties by this means alone and it is altogether insufficient in the varicose type and the bronchiectatic abscess. In these conditions bronchoscopic drainage is essential. It should be stressed that drainage in itself never cures the ectasia irrespective of its form; it affords only symptomatic relief. Intrabronchial treatment in conjunction with intravenous antisyphilitic treatment in cases of the globular type of bronchiectasis deserves clinical trial.

Artificial pneumothorax is effective only in cases of bronchiolectasis which yields even to a low tension compression. If the lesion is limited to one lobe, a selective type of pneumothorax which entails little discomfort to the patient [19] can be created. However, the therapeutic value of artificial pneumothorax is questionable in cases of cylindric or varicose bronchiectasis, as the rigid area will not yield to a collapse of a

17. Bendove, R. A.: Silent Pulmonary Cavities; Their Probable Mechanism, Diagnosis and Prognosis, J. A. M. A. **87**:1739 (Nov. 20) 1926; Roentgenology as an Investigational Field in the Mechanism of Physical Signs of the Chest, Am. J. M. Sc. **173**:322, 1927.

18. Ochsner, A.: Use of Iodized Oil in the Treatment of Bronchiectasis, S. Clin. North America **10**:843, 1930.

19. Bendove, R. A.: Selective Therapeutic Pneumothorax in Acute Pulmonary Suppuration, Am. J. Surg. **19**:49, 1933.

safe degree of tension. Still, pneumothorax may change the lobe and its ectatic bronchi from a vertical to a horizontal position and thus promote better drainage. Artificial pneumothorax often finds its use as a preparatory procedure to radical thoracic operations.

Medical treatment is of no value in cases of marked suppurative bronchiectasis with complete destruction of the bronchial wall; the sooner surgical treatment is used in such cases, the better are the chances for clinical improvement.

SUMMARY

Recent studies of the respiratory dynamics of the bronchi and their defensive or expulsive mechanism are briefly reviewed, and the physiopathologic changes which may precede or accompany bronchial dilatation are discussed with especial reference to their diagnostic significance in early bronchiectasis.

Six distinct morphologic types of bronchial dilatation, five of which are bronchiectatic and one of which is bronchiolectasis, are described as visualized roentgenologically after the intrabronchial injection of iodized oil. They are: the tubular, cylindric, varicose and globular types, bronchiolectasis and bronchiectatic abscess.

The various theories concerning the mode of production of the polymorphic varieties of bronchiectasis are advanced, and the probable pathogenesis of each type is discussed. The tubular form may result from prolonged irritation of the bronchial mucosa; sclerotic and degenerative changes of the myo-elastic layers are considered to be the primary lesion in the cylindric form; the varicose type is, as a rule, brought about by massive pulmonary cirrhosis or atelectasis, whereas a diffuse bronchopulmonary distribution of fibrosis may entail bronchiolectasis; the globular type is only a segmental pouching occasioned by local weakening in the bronchial wall, and the primary bronchiectatic abscess is initiated by suppurative lesions in the bronchi.

Each of these morphologic types reveals itself clinically by a different mode of onset, a variable train of symptoms and certain physical signs. The clinical history is of greater diagnostic value than are the physical signs. Further studies and closer correlation between symptoms, signs and morphologic aspects as outlined by iodized oil in the living will no doubt enable us to draw a sharper line of clinical demarcation between the various forms.

No diagnosis of bronchiectasis is complete unless the location, the distribution and, above all, the type have been determined, for on this information often depends the therapeutic procedure to be followed. The indications for certain therapeutic measures in the various types are briefly discussed.

OSTEOMALACIA

NECROPSY OBSERVATIONS IN A MAN

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AND
WALTER H. NADLER, M.D.
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Interest in the group of diseases characterized by diffuse demineralization of the bones has been stimulated within the last decade by the increase in knowledge of calcium metabolism brought about by the studies of Aub and his co-workers, by the demonstration of the rôle played by vitamin D and, notably, by the discovery of parathormone. The preparation by Collip [1] of a potent extract of the parathyroid glands made possible the establishment of clinical criteria for the diagnosis of hyperparathyroidism. That Recklinghausen's disease (osteitis fibrosa cystica) is due to parathyroid tumor and is relieved by parathyroidectomy was first demonstrated by Mandl; [2] subsequent investigations have established that the clinical symptoms of this disease are dependent on hyperparathyroidism.

Genuine osteomalacia is a rare disease, particularly in males. Recent studies indicate that deficiency in vitamin D is primarily responsible. The metabolic changes characteristic of hyperparathyroidism have not been demonstrated. Enlargement of the parathyroid glands may, however, be present. Hypertrophy and hyperplasia, first described in cases of osteomalacia by Erdheim [3] in 1906 and interpreted as an effect of the disease, have been reported in many but not in all cases. The observations at necropsy in a severe case of long standing seem of interest.

From the Departments of Pathology and Medicine, Northwestern University Medical School.

1. Collip, J. B.: The Extraction of a Parathyroid Hormone Which Will Prevent or Control Parathyroid Tetany and Which Regulates the Level of Blood Calcium, J. Biol. Chem. **63**:395, 1925.

2. Mandl, F.: Therapeutischer Versuch bei einem Falle von Osteitis fibrosa generalisata mittels Extirpation eines Epithelkörperchentumors, Zentralbl. f. Chir. **53**:260, 1926.

3. Erdheim, J.: Tetania parathyreopriva, Mitt. a. Grenzgeb. d. Med. u. Chir. **16**:632, 1906.

REPORT OF CASE [4]

The patient was a white man whose parents were Americans in average circumstances. The first sign of the disease, pain and deformity in the chest, appeared when he was about 19 years of age. Pains in the back, chest and hips became severe about three years later and led him to seek medical advice. At this time the deformity in the chest was marked. A history of a deficient diet could not be obtained. Treatment for a year produced no improvement. In 1911, when the patient was 23 years of age, castration was performed. The testes were normal. Prolonged treatment with phosphorus, trials of thyroid extract, extract of the posterior lobe of the pituitary gland and epinephrine and adherence to a general diet to which were added large amounts of milk and leafy vegetables, resulted in subjective improvement, which was maintained for the next ten years so that he was able to carry on his work of watch repairing. He was unable, however, to walk without crutches. The condition of the bones remained unchanged as determined by clinical and roentgen examinations. Repeated physical examinations during this period revealed only the characteristic softness of the bones and the resulting deformity. No palpable enlargement in the thyroid region was ever observed. The basal metabolic rate was normal, and symptoms of hyperthyroidism were lacking except for a brief period following the use of extract of thyroid gland. The patient was last examined in 1921. A severe infection of the upper respiratory tract in January, 1928, was followed by cardiac decompensation. After seven weeks in bed he died in March, 1928, at the age of 40. Roentgenograms of the chest, spine, pelvis and extremities made post mortem showed an extreme loss of calcium, much more marked than had previously been observed, and an absence of cysts or tumors in the bones (fig. 1).

Necropsy.—The body was that of a poorly nourished white man, appearing to be much younger than the actual age given (40 years). The length of the body when the knees were forcibly extended was about 59 inches (150 cm.); the weight was about 90 pounds (40.9 Kg.). The upper part of the thoracic spine showed a prominent kyphosis which extended backward and to the right; the lumbar vertebrae, a compensatory lordosis and scoliosis. The anterior wall of the chest presented an exaggerated degree of pigeon breast deformity. The horizontal rami of the pubis were bent inward, producing a beaklike prominence of the symphysis and an extremely narrow pubic arch. There was a lateral angulation of the right humerus at the junction of the middle and lower thirds, and the left humerus showed a similar, but less prominent, deformity. The proximal phalanges of both hands were in the position of hyperextension. The metacarpophalangeal joints and the knees and ankles were greatly enlarged. The loose knee joints and enlarged external condyles of the tibias and femurs produced an apparent angulation at the knees, which were held in a semiflexed position by the shortened hamstring muscles.

The calvarium was extremely light weight, with resistance to sawing like that of soft, dry wood. In its thickest part it measured 8 mm. and in its thinnest, 4 mm. A groovelike depression involving only the outer table of the left side of the frontal bone was located just beneath a thin scar of the forehead. Transverse sections through the femur and tibia about 20 cm. and 25 cm., respectively, from the knee joint showed a soft, friable shell of bone from 0.5 to 1 mm. in thickness.

4. A clinical description of this case was reported in 1917 (Elliott, C. A., and Nadler, W. H.: The Effect of Castration upon Osteomalacia in the Male, Am. J. M. Sc. **153**:722, 1917).

The marrow consisted of yellow fat. The cancellous part of the bones near the joint was so soft that it could be indented with the thumb-nail. The bone of the vertebral bodies was somewhat firmer. The ribs were extremely soft and brittle. They could be cut smoothly with a knife, and some portions seemed to be completely decalcified. Enlargements which represented the sites of old fractures were composed of fairly dense rubbery fibrous tissue, but they were elastic, could be

Fig. 1.—Roentgenogram of the right humerus showing the characteristic demineralization and a spontaneous fracture.

compressed between the fingers and appeared to contain no calcium salts. Many of these were seen from the inside of the wall of the chest. Some were angulated, while others showed merely callus-like thickenings.

The endocrine glands revealed nothing of importance except slight hypertrophy of the hypophysis (0.95 Gm.) and hypertrophy of the two parathyroid glands. The thyroid gland weighed 28.5 Gm., was symmetrical and showed a homogeneous,

glistening, yellow-red parenchyma. On the posterior margin of each lobe, about 2 cm. from the upper pole, was a yellow-gray parathyroid body outside the thyroid capsule. Their measurements were, respectively, 11 by 4 by 2 mm. and 10 by 7 by 2 mm. The others were not visible on the surface, and serial free-hand sections made from 1 to 2 mm. apart after hardening the gland in a solution of formaldehyde failed to reveal the other two parathyroid bodies. The suprarenal glands weighed 13 Gm. together and on section showed a normal bright yellow and light brown cortex about 1 mm. in thickness and a gray medulla in normal proportion. The pancreas was not remarkable. Both testes were missing and had been replaced by balls of paraffin.

The pathologic findings in the other organs and tissues are included in the following anatomic diagnosis: osteomalacia with extreme deformities of the spine, thoracic cage, pelvis and bones of the extremities; multiple old healed fractures of

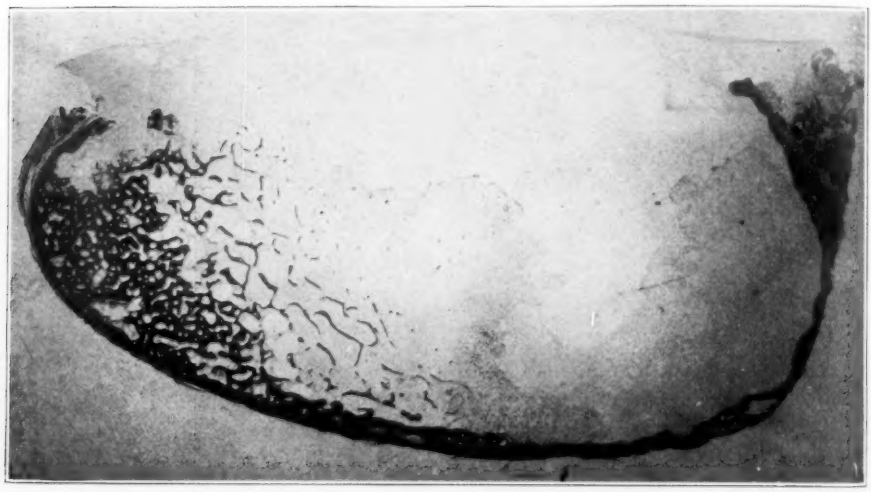

Fig. 2.—A transverse section through the shaft of the tibia about 12 cm. from the knee joint, to show the thin cortex and the reenforcing mass of cancellous bone in the anterior portion. The marrow is entirely fatty. The decalcified section was set in a concentrated form of pyroxylin. Hematoxylin-eosin stain; × 3.6.

the ribs and humeri; hypertrophy of the two parathyroid glands; slight hypertrophy of the hypophysis; fatty degeneration of the myocardium, and hypertrophy and dilatation of the right ventricle of the heart; brown induration and compression atelectasis of the lungs; chronic passive hyperemia and moderate atrophy of the liver; bilateral hydrothorax; hydropericardium; chronic ulcer of the pyloric portion of the stomach; absent testes, and high grade general emaciation.

Histopathology.—Bones: Decalcified tissue was embedded in a concentrated preparation of pyroxylin and stained with hematoxylin and eosin and hematoxylin and carmine. Sections from the condyles of the femur through the articular cartilage showed a smooth, regular layer of eosinophilic hyaline cartilage on the outside which measured 1.5 mm. in thickness. Near its inner margin was an interrupted

narrow band containing apparently normal cartilage cells with a purple matrix (calcified cartilage); a similar band of irregular patches of purple (calcified) cartilage formed a transitional zone between the hyaline cartilage and the bone. There was no regular bony cortex in this location, but merely the edges of irregular thick trabeculae of cancellous bone. The central part of the bone was formed of these irregular thick trabeculae and a fatty, fibrous marrow. Cellular marrow was found only in small islands in the zone of ossification, and the nucleated elements in these foci were chiefly nucleated red blood cells. The edges of the bony trabeculae were smooth in most places, and the borders were formed by wide zones

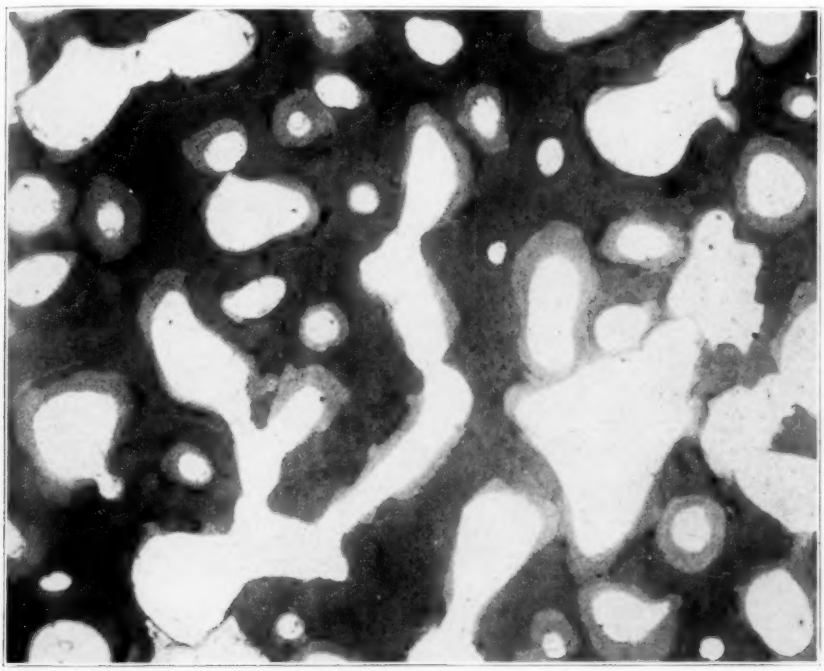

Fig. 3.—A low power (× 40) photomicrograph of a cancellous portion of the tibia shown in figure 2. The light borders lining the trabeculae and surrounding the haversian canals are the calcium-free "osteoid seams."

of strongly eosinophilic bone laid down in regular lamellae. The middle zones of the trabeculae contained variously shaped, poorly defined areas that stained more or less strongly with hematoxylin (calcified areas). These calcified areas lay in regions that contained few Volkmann's canals, and in only a few places did they border on the medullary spaces. In general there was little evidence of active formation or destruction of bone. A few exceptions were found, however, in the form of large and small lacunae surrounded by bone with jagged edges, partly lined by regular rows of osteoblasts and showing nearby a few multinucleated giant cells (osteoblasts). The marrow in the lacunae was in some instances, fibrous and in others fatty with small hemorrhages.

Transverse sections of the tibia and femur showed a fairly dense cortex of varying thickness (from 0.5 to 1.5 mm.). The periosteum was essentially normal and the periosteal surface of the cortex was smooth, while the endosteal line was wavy. In the thicker segments large medullary spaces were enclosed between the endosteal and periosteal lamellae. There was a greater proportion of calcified bone in these sections than in those previously described. The calcium-poor (eosinophilic) portions formed narrow zones along the endosteal surfaces and broader zones around the haversian canals and around most of the medullary spaces. Anteriorly the thin cortex of the femur was reinforced by cancellous bone of a

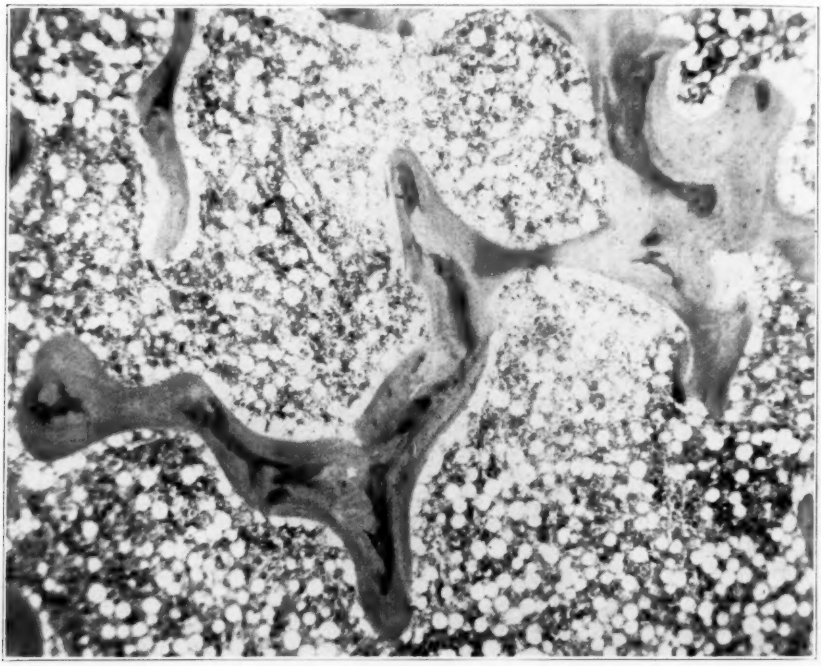

Fig. 4.—Photomicrograph (× 40) of cancellous bone from a vertebral body. The "osteoid seams" are extremely wide. Only the dark patches along the middle portions of the trabeculae are calcified.

finer texture than that of the region of the condyles. The marrow consisted entirely of fat (figs. 2 and 3).

The vertebral bodies (fig. 4) were composed of very coarse anastomosing trabeculae which showed in their central portions narrow streaks and irregular patches of purple (areas of calcification) and broad zones of eosinophilic (calcium-free or calcium-poor) bone bordering the medullary spaces. The spaces contained a normal proportion of cellular marrow. Scattered through the marrow were poorly outlined masses of homogeneous purplish-gray acellular tissue resembling degenerated osteoid tissue. The zone of ossification between the cartilaginous plate

and cancellous bone was irregular, and in some places the intervertebral disk contained islands of poorly formed cancellous bone.

Sections of the ribs made longitudinally through sites of old fractures showed dense callus consisting of broad, slightly calcified bony trabeculae, small islands of cartilage and poorly cellular fibrous tissue. On each side of the callus the marrow was unusually rich in hematopoietic tissue; within the callus it was largely fatty and fibrous.

Heart: Sections from the wall of the left ventricle and muscular septum showed swollen, granular muscle fibers with shrunken, irregular, hyperchromatic nuclei in many areas. In the right ventricle the degenerative changes were much more advanced. Between the pectinate muscles of the right auricle small thrombi were insinuated; in several places they were intimately attached to the endocardial surface. Frozen sections stained with sudan III and hematoxylin showed small irregular patches and stripes of yellow lipoid substance intermingled with fewer coarse red granules of fat within the degenerated segments of muscle fibers. These areas of fatty degeneration were extremely numerous in the wall of the right ventricle and constituted as much as 50 per cent of the area represented.

Lungs: The parenchyma showed the effects of compression and stasis in the form of flattening of the alveoli, thickening of their walls and large numbers of macrophages and erythrocytes within the narrow alveolar spaces. Several foci of lymphocytic infiltration were found near the small bronchi.

Liver: The most prominent histologic changes appeared in the parenchyma around the dilated central veins. The hepatic cords around them were extremely slender and in many instances had disappeared, leaving only the radially arranged sinusoidal endothelium and granular cellular débris. The remaining cells had pyknotic nuclei and scanty cytoplasm filled with finely granular brown pigment. A large number of the hepatic cells in the intermediate zone contained small vacuoles, but at the peripheries of the lobules they were essentially normal.

Spleen and Kidneys: There was a slightly increased density of the fibrous reticulum in the spleen. The sinusoids were moderately distended with blood. The glomeruli of the kidneys were uniformly large. The convoluted tubules showed a moderate to high grade granular degeneration, with thinning of the epithelium, pyknosis of many of the nuclei and much granular detritus in the lumens. The cortex contained numerous small calcareous deposits, most of which appeared to lie within lymph channels, sometimes near a glomerulus and occasionally at some distance from any glomerulus in the section. A few clumps were found between the collecting ducts in the papillae.

Suprarenal Glands. In routine sections stained with hematoxylin and eosin the cortex showed nothing abnormal. The chromaffin tissue of the medulla was unusually abundant. Frozen sections stained with hematoxylin and sudan III showed abundant stainable lipoid substance throughout the cortex; many of the coarser droplets had the staining reaction of neutral fat.

Hypophysis: In the anterior lobe the sinus-like blood capillaries were widely dilated (postmortem settling?). In general the chief cells predominated. Near the center of the lobe eosinophilic and chief cells appeared to be in about equal numbers, while at the periphery the latter constituted by far the greater part of the parenchyma. The basophilic cells were concentrated in poorly outlined masses in the anterior and inferior part of the lobe near its apex, and their number was relatively very small. Tissue fixed in a solution of formaldehyde and stained with ethyl-violet-orange G after mordanting in potassium dichromate yielded essentially the same findings as tissue stained in hematoxylin and eosin after fixation in

Zenker's solution to which a solution of formaldehyde has been added. No differential counts were made of the specifically stained cells since careful comparisons with sections of normal hypophyses demonstrated to our satisfaction that this picture was well within the limits of normal variation. The pars intermedia was not well developed and was represented by only a few follicles containing colloid substance and was lined by a single layer of low cuboid epithelium. The pars nervosa showed no noteworthy changes.

Pineal Gland: The structure was that of a normal adult gland, with masses of calcareous matter near the line of junction between the pedicle and the glandlike structures.

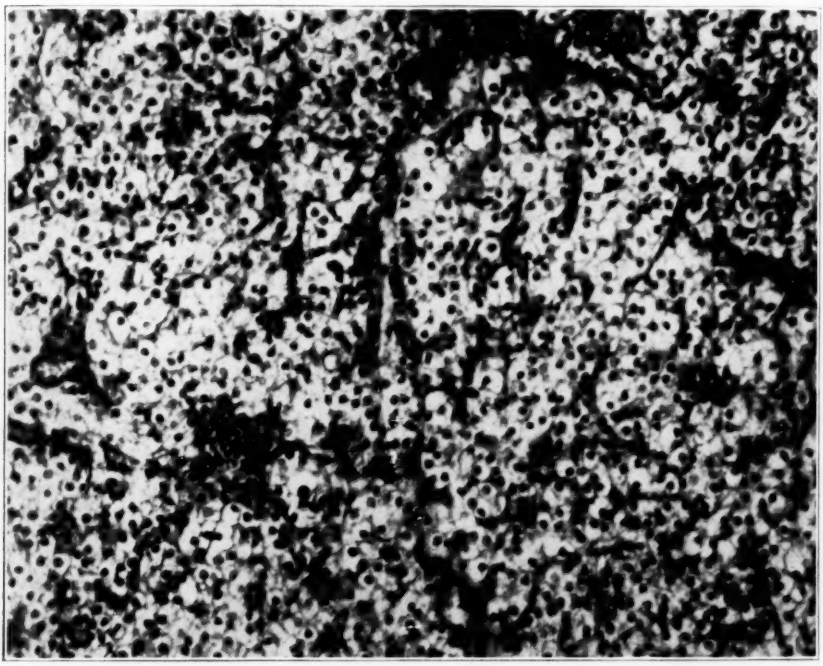

Fig. 5.—A high power (× 200) photomicrograph of a section of one of the parathyroid glands. The chief cells predominate. A few scattered eosinophils are seen near the blood vessels as cells with dark gray cytoplasm.

Thyroid Gland: This was essentially normal.

Parathyroid Glands: Each of the two glands was completely surrounded by a delicate fibrous capsule, and the structure of the parenchyma did not differ appreciably from that of a normal parathyroid body. The polyhedral epithelial cells were packed together in solid lobules and cords, and in a few small areas alveolar structures were formed by columnar cells which differed only in shape from the polyhedral cells. The cytoplasm was clear or very finely granular. The nuclei were nearly round and dark and showed a sharp nuclear membrane and fine

chromatin granules. In a few small, poorly defined areas the cells were swollen and the cytoplasm was foamy or entirely clear. In other areas of similar extent but more sharply outlined the cytoplasm was strongly eosinophilic and finely granular. The eosinophilic cells were found also singly or in small groups scattered throughout the glands. Their nuclei were slightly smaller and darker than those of the predominant pale cells. Interstitial fat was very scanty as compared with the amount usually found in normal glands. Relatively large areas showed none. The usual close network of fine blood capillaries was found; the capillaries seemed neither more engorged nor less well filled than under normal conditions.

Fig. 6.—Another area from a section of the parathyroid gland, including a small mass of eosinophil cells in the upper right hand corner (× 150).

COMMENT

This case of severe osteomalacia in a man apparently began at about the age of 19 and continued for twenty-one years. During eleven years of observation no significant findings other than the changes in the bones were observed. There was no palpable tumor in the region of the thyroid gland; evidence of hyperthyroidism was lacking. No history of dietary deficiency was obtained. Accurate clinical studies of the calcium metabolism were not possible prior to 1921, when the

patient was last examined. Castration in 1911 had no appreciable effect; in the week following the operation the excretion of calcium and phosphorus in the urine and feces was approximately the same as before the operation. The condition remained stationary for a number of years. Pathologic fractures occurred late in the disease. Death was due, probably, to heart failure. Necropsy showed fatty degeneration of the cardiac muscle, chronic passive congestion of the liver, parenchymatous degeneration of the kidneys, and generalized rarefaction and decalcification of the skeleton without formation of a cyst or tumor.

An unquestionable differentiation between osteomalacia and Recklinghausen's disease in certain cases does not appear to be possible on the basis of changes in bone alone. While in advanced cases of the latter disease cystic areas or brown tumors (hemorrhagic giant cell tumors) or both can usually be demonstrated, there are some cases in which these features are lacking.[5] Histologically the wide osteoid seams of trabeculae, the absence of excessive fibrosis of the marrow, and the relatively small number of osteoblasts in true osteomalacia tend to distinguish it from typical Recklinghausen's disease, in which the osteoid seams are narrow, fibrosis of the marrow is a striking feature, and both osteoblasts and osteoclasts are numerous, frequently with the formation of giant cell tumors. However, these differentiating features are only relative, and the degree of development of each depends on such factors as the intensity and duration of the disease, the diet of the patient and the therapeutic measures used. In a recent review of the subject of hyperparathyroidism Jaffe [6] suggested that one of Erdheim's cases described in 1907,[7] the first one of the series in which an enlarged parathyroid gland was shown, was not really one of osteomalacia but one of Recklinghausen's disease because of the narrow osteoid borders, fibrous marrow and numerous osteoblasts in the involved bones. In our case also some parts of the marrow were fibrous, and in a few areas both osteoblasts and osteoclasts were numerous, but the consistently wide osteoid borders would certainly furnish strong evidence that the case was one of osteomalacia and not of osteitis fibrosa.

In the case reported the glands of internal secretion were normal grossly and microscopically with the exception of the hypophysis and parathyroid glands. The hypophysis showed slight hypertrophy, but without selective hyperplasia of any one type of cell. The parathyroid glands were only two in number, each definitely enlarged, being 11 by

5. Bergstrand, H.: Acta med. Scandinav. **54**:539, 1921.

6. Jaffe, Henry L.: Hyperparathyroidism (Recklinghausen's Disease of Bone), Arch. Path. **16**:63 (July) and 236 (Aug.) 1933.

7. Erdheim, J.: Sitzungsb. d. k. Akad. d. Wissensch. Math. naturw. Kl., Wien. **116**: 311, 1907.

4 by 2 and 10 by 7 by 2 mm. as compared with an average normal size of 6 by 3 by 2 mm.[8] Microscopically the only definite deviation from normal was the poverty of fat cells. Such a reduction of fat is generally considered evidence of hyperplasia of the parenchyma. The other measure of hyperplasia, originally used by Erdheim[9] to demonstrate microscopic hyperplasia in glands of normal size or slight enlargement—i. e., the demonstration of lipoid droplets in the parenchymal cells by treating the tissue with osmic acid after fixation in Altmann's fluid—was not utilized in this case as the two entire glands had been embedded in paraffin before it occurred to us that such treatment might be desirable. The foamy appearance of small clumps of cells in the paraffin sections suggested that a considerable amount of lipoid had been present, and therefore it is unlikely that the degree of hyperplasia indicated by such a criterion is more than moderate. Furthermore, later work has cast doubt on the validity of such a criterion of hyperplasia, i. e., paucity of lipoid in the presence of active hyperplasia.[5]

The presence in this case of slight calcareous deposits in the kidneys without associated necrosis of the cells is consistent with the findings reported in many other cases of osteomalacia. Frequently other tissues in which acid is excreted, such as the lungs and the stomach, have been similarly involved. The explanation is not clear. In osteitis fibrosa such precipitation of calcium is naturally considered to be related to hypercalcemia.[10] In the cases of osteomalacia that have been studied, however, an elevated calcium level in the blood has not been observed at any stage. In cases in which no treatment has been given the negative calcium balance reported has been due chiefly to the increased elimination of calcium in the feces.[11] On a diet low in calcium, however, a urinary excretion of calcium greater than the intake has been observed.[12] It appears that in osteomalacia hyperplasia of the parathyroid glands represents a compensatory physiologic hyperactivity of these glands resulting in such gradual loss of bone calcium that hypercalcemia does not occur. The mechanism seems to be similar to that of experimental rickets in which deficiency of vitamin D causes hypertrophy and hyperplasia of the parathyroid glands. Prevention of hyper-

8. Cowdry, E. V., in Barker, L. F.: Endocrinology and Metabolism, New York, D. Appleton & Company, 1922, vol. 1, p. 501.

9. Erdheim, J.: Beitr. z. path. Anat. u. z. allg. Path. **33**:158, 1903.

10. Bulger, H. A.; Dixon, H. H., and Barr, D. P.: The Functional Pathology of Hyperparathyroidism, J. Clin. Investigation **9**:143, 1930.

11. Miles, L. M., and Feng, C.: Calcium and Phosphorus Metabolism in Osteomalacia, J. Exper. Med. **41**:137, 1925.

12. Gargill, S. L.; Gilligan, D. R., and Blumgart, H. L.: Metabolism and Treatment of Osteomalacia, Arch. Int. Med. **45**:879 (June) 1930.

trophy of the parathyroid glands by the administration of parathormone in minor deficiency of vitamin D produced experimentally has been reported.

The symmetrical enlargement and normal histologic appearance of the parathyroid glands in this case are convincing evidence that the condition was simple hyperplasia rather than neoplasia (adenoma). We are inclined to consider the hyperplasia compensatory in the sense of Erdheim and the majority of later authors. This is consistent with the findings in a number of cases of true osteomalacia reported in the literature since Erdheim's publications of 1906 and 1907. Such an opinion is supported by the fact that compensatory enlargement of the parathyroid bodies occurs frequently in other diseases associated with rarefaction of bone, such as rickets, senile osteoporosis, so-called hunger osteomalacia, chronic nephritis and both primary and secondary tumors of bone.

Clinically, hyperparathyroidism associated with parathyroid tumor has been proved to be an entity embracing Recklinghausen's disease. Conservative application of present knowledge limits the indication for parathyroidectomy to primary hyperparathyroidism. The persistence after operation of definite signs of the disease points to the presence of an undiscovered hyperfunctioning tumor. The tentative classification of other conditions of varied etiology, such as rickets, osteomalacia and loss of calcium from the bones in cases of hyperthyroidism and pregnancy, as secondary hyperparathyroidism has been confusing. It has been suggested that the parathyroid glands which progressively remove calcium from the bones in order to maintain a normal level of calcium in the blood may continue to remove excessive amounts long after the need has passed, and that excision of glands which prove to be normal on gross and microscopic examination is justifiable when clinical findings signify overactivity.[13] From the information available, however, it appears unlikely that the removal of glands found to be normal will, per se, have a beneficial effect. The problem is one of accurate diagnosis and location of the tumor.

The diagnosis of osteomalacia depends (1) on the differentiation of primary hyperparathyroidism and (2) on the exclusion, in adults, of osteoporosis occurring in hyperthyroidism, senility, neoplasms involving bones, etc. In typical advanced cases of Recklinghausen's disease the following observations are diagnostic: a high level of serum calcium and an excessive excretion of calcium in the urine; a low concentration of serum phosphorus and an increased elimination in the urine; roentgenographic evidence of a diffuse loss of calcium

13. Hitzrot, L. H., and Comroe, B. I.: Hyperparathyroidism Without Parathyroid Tumor, Arch. Int. Med. **50**:317 (Aug.) 1932.

from the bones, usually with formation of cysts or tumors; hypotonia and muscular weakness. Difficulty is encountered in early cases in which cysts or tumors of bone are absent. The parathyroid tumor, involving one or more glands, is frequently not palpable; detection may require exposure of each of the glands. Persistent hypercalcemia associated with a lowered level of phosphorus is decisive. Hypercalcemia was consistently present in the seven cases of osteitis fibrosa observed by Bauer.[14] Under certain conditions of diet and therapy, however, the level of the blood calcium may not be elevated.[6] Such cases require prolonged and carefully controlled metabolic studies.

That deficiency of vitamin D is the essential cause of osteomalacia is indicated by various studies. Miles and Feng,[11] in 1925, reported a marked seasonal variation in the severity of the condition in cases observed in China. They found a negative calcium balance in three of four cases, obtained good results with the administration of cod liver oil and calcium, and concluded that the disease was one of dietary deficiency in the same category as rickets. The case of Gargill, Gilligan and Blumgart,[12] carefully studied for more than a year, showed a persistently normal level of blood calcium and a lowered level of blood phosphorus, a finding which is present also in rickets. A negative calcium balance persisted, even though the intake of calcium greatly exceeded normal requirements, until the patient was fed very large amounts of cod liver oil concentrate. The addition of irradiation with ultraviolet rays hastened the improvement. These results suggested that the condition was a form of adult rickets. Viosterol and calcium therapy have also been used with benefit.[15]

SUMMARY

The observations of necropsy in a typical case of osteomalacia in a man are presented and discussed. Besides the typical skeletal deformities, the pathologic changes of special interest were hypertrophy and hyperplasia of the parathyroid glands, slight hypertrophy of the anterior lobe of the hypophysis and numerous small calcareous deposits in the kidneys. Only two parathyroid glands could be found. These were equally enlarged and presented microscopic evidence of mild hyperplasia interpreted as a compensatory condition caused by increased physiologic activity.

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14. Bauer, W.: Hyperparathyroidism: A Distinct Disease Entity, J. Bone & Joint Surg. **15**:135, 1933.

15. Decourt, J., and Kaplan, S.: Le traitement de l'ostéomalacie par l'ergostérol irradié, Paris méd. **2**:485 (Dec. 3) 1932.

News and Comment

AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians will hold its nineteenth annual clinical session in Philadelphia from April 29 to May 3, 1935. Announcement of these dates is made not only to apprise physicians generally of the meeting, but also to prevent conflicting dates for the 1935 meetings of other societies.

Dr. Jonathan C. Meakins, of Montreal, Canada, is president of the American College of Physicians, and will arrange the program of general sessions. Dr. Alfred Stengel, vice president in charge of medical affairs of the University of Pennsylvania, has been appointed general chairman of local arrangements, and will be in charge of the program of clinics. Mr. E. R. Loveland, executive secretary, 133-135 South Thirty-Sixth Street, Philadelphia, is in charge of general and business arrangements, and may be addressed concerning any feature of the forthcoming session.

Book Reviews

A System of Clinical Medicine: Dealing with the Diagnosis, Prognosis, and Treatment of Disease; for Students and Practitioners. By Thomas Dixon Savill, M.D. Edited by Agnes Savill, M.D., assisted by E. C. Warner, M.D. Ninth edition. Price, $9. Pp. 1,063, with 163 illustrations. Baltimore: William Wood & Company, 1933.

The ninth edition of this system of clinical medicine makes its appearance twenty-eight years after the first edition was brought out. The work has evidently been well received and must have a certain amount of inherent merit to have survived so many editions over such a period of time and with the original editor supplanted by another. The book represents the work not of one man but rather of some seventeen contributors, who have prepared certain sections or revised certain portions. The list of contributors includes the names of some well known English physicians, names which are a guarantee of the reliability of the work.

The material is presented in rather an unusual way. The editor wanted to stress clinical medicine; therefore the classification of diseases is based largely on their clinical expressions. An excellent example is found in the classification of diseases of the lungs and pleurae. Roughly, these are divided into acute and chronic conditions and further subdivided into those that occur (1) without dulness on percussion, (2) with dulness on percussion and (3) with hyperresonance. Such a classification may call attention to, and accentuate, the most outstanding physical sign or symptom, but it makes for a jumbled hotchpotch which is unwieldy and which is dogmatic. Dogmatism is rife throughout the book; for example: "A patient complains of pain in the gall-bladder region; pain is paroxysmal or dull and continuous, and radiates to the right shoulder. There is tenderness over the gall-bladder, vomiting and some fever. The disease is acute cholecystitis." Such dynamic diagnoses may make medicine simple to the student, but, unfortunately, in practice the diagnosis of pathologic conditions is not made with the ease implied in this statement and similar statements.

The book deals with many phases of internal medicine other than disease entities. It starts with a brief discussion of case taking and methods; a section on physical diagnosis follows. The discussion of each anatomic system is preceded by a brief account of the symptoms that arise as a result of disease of this particular system. Here and there some effort is made to explain the pathologic physiology of the underlying disorder. Elsewhere will be found a number of pages devoted to diets. Then comes a section giving general information concerning laboratory examinations; this is too brief to be of practical use, but it will give the reader who is unfamiliar with these examinations some understanding of their purpose and value. The concluding section deals with a list of about eighty-one prescriptions for all kinds of conditions, varying from a solution of lead with zinc to a tannic acid gargle and to an expectorant cough mixture for children.

The book decidedly gives one the impression of being old-fashioned; it is entirely too dogmatic to appeal to any one except the most inexperienced tyro in the study of medicine, on whose mental processes it might produce grave injury; it attempts to cover too much ground in too few pages.

Nature, M.D. By Richard Kovacs, M.D., Clinical Professor of Physical Therapy, New York Polyclinic Medical School and Hospital. Price, $2. Pp. 181, with 10 illustrations. New York: D. Appleton-Century Company, 1934.

This volume is one of the so-called Popular Health Series, volumes of which are being published from time to time by the Appleton-Century Company. It is an unassuming book, not too long, well printed and written, as the author states,

in the hope that laymen, as well as professional persons who are interested in the remedial uses of heat, water, sunlight, electricity, massage and exercise, will find the information offered helpful.

It must be difficult to assemble a book dealing with medical matters which will interest the casually reading public and yet be of some use to physicians. This book has accomplished this task with a surprising degree of success. The ordinary physician, in general, knows little about the details of physical therapy. Here he has a chance to learn something of the theory and practice behind the popular forms of treatment which nowadays he often prescribes for his patients. On the other hand, the layman will find nothing to pander to morbid curiosity. He is given straightforward and honest information in regard to matters now familiar to him from well planned advertising, such as electric baths, bottled sunshine and colonic irrigations. On the whole, the book is worth owning.

Alcohol: Its Effects on Man. By Haven Emerson, M.D., Professor of Public Health Practice, Columbia University. Price, $1. Pp. 114. New York: D. Appleton-Century Company, 1934.

This manual has been written to provide school teachers and high-school and college students with authoritative information regarding the effects of alcohol on man, as these are now known to medical science. It is written with particular simplicity, from a nonpartisan point of view, and the essential facts of the present knowledge regarding this subject are summarized.

The underlying purpose in preparing a book of this character is summed up in the concluding sentence: "If the school children of the next few decades are taught the facts about alcohol as these are known, through the use of the scientific and experimental methods of the medical and social sciences, they and their children will be in a position to determine a rational personal and governmental attitude towards commerce in, and beverage use of, alcohol, and they may then avoid the extremes of partisanship in argument, the pitfalls of political exploitation of voters, and the misinterpretation of knowledge by commercial interest and the press, which together have made so pitiful an exhibition of our people during the past twenty years." The book can be highly recommended and will be helpful to the readers for whom it is intended.